UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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NEUROLOGICAL DEVICES PANEL

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March 18, 2011
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

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ROBERT W. HURST, M.D.	Chair
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ANDREW KU, M.D.	Temporary Voting Member
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M E E T I N G

(8:00 a.m.)

DR. HURST: I'm Dr. Robert Hurst, the Chairperson of the Panel. I'm an interventional neuroradiologist at University of Pennsylvania, Professor of Neurosurgery, Neurology, Radiology at the University of Pennsylvania.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 24. I'd also like to add the Panel members participating in the meeting today have received training in FDA law and regulations.

For today's agenda, the Panel will discuss, make recommendations, and vote on information related to premarket approval application for the Pipeline Embolization Device, sponsored by Chestnut Medical. The Pipeline Embolization Device is indicated for the endovascular treatment of large or giant wide-necked intracranial aneurysms in the paraclinoid region of the internal carotid artery.

Before we begin, I'd like to ask our distinguished Panel members and FDA staff seated at the table to introduce yourselves. Please state your name, your area of expertise, your position and affiliation, and I'd like to start on my right with Dr. Brem.

DR. BREM: Henry Brem, Professor of Neurosurgery, Ophthalmology, Oncology, and Biomedical Engineering, and Chairman of the

Department of Neurosurgery at Johns Hopkins.

DR. KANG: Peter Kang. I'm the director of the EMG Laboratory at Children's Hospital, Boston, and I'm a pediatric neurologist.

DR. RICHARDSON: Don Richardson. I'm a Professor of Neurosurgery and Biomedical Engineering at Tulane University, New Orleans.

DR. POSNER: Phil Posner. I'm the Patient Representative, and I'm a retired Professor of Physiology, Pharmacology, and Neuroscience at University of Florida, Auburn, and Florida State Universities.

DR. BECKER: And I'm Kyra Becker. I'm a vascular neurologist, Professor of Neurology and Neurological Surgery at the University of Washington in Seattle.

DR. DUEHRING: Gary Duehring, Professor of Healthcare Administration, Central Michigan University.

MR. MUELLER: David Mueller. I am the Industry Representative, and I teach regulatory affairs at several universities, and I'm also in regulatory affairs currently at American Medical Systems.

DR. EYDELMAN: Good morning, and welcome. I'm Malvina Eydelman. I'm the Director of the Division of Ophthalmic, Neurological, and ENT Devices at the FDA.

DR. BYRNE: Rich Byrne. I'm Professor and Chairman of Neurosurgery at Rush University Medical Center in Chicago.

DR. KU: Andrew Ku, interventional neuroradiologist at

Allegheny General Hospital, Pittsburgh, Pennsylvania.

DR. YANG: Good morning. I'm Lynda Yang. I'm a neurosurgeon at the University of Michigan.

DR. EVANS: Good morning. Scott Evans, Senior Research Scientist, Biostatistics, Harvard University.

DR. CLAUDIO: Olga Claudio, Designated Federal Officer for the Neurological Devices Panel, Food and Drug Administration.

DR. HURST: Thank you. If you've not already done so, please sign the attendance sheets that are on the tables by the doors.

Dr. Olga Claudio, the Designated Federal Officer for the Neurological Devices Panel, will make some introductory remarks.

DR. CLAUDIO: Good morning. I will now read the Conflict of Interest Statement, particular matter involving specific parties.

The Food and Drug Administration is convening today's meeting of the Neurological Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but

not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of the Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's service outweighs his or her potential financial conflict of interest. Under Section 712 of the Federal Food Drug and Cosmetic Act, Congress has authorized FDA to grant waivers to special Government employees and regular Government employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

Today's agenda involves a discussion on issues relevant to a

premarket approval application sponsored by Chestnut Medical Technologies, Inc., for the Pipeline Embolization Device. The Pipeline Embolization Device is an implanted mesh cylinder intended for the embolization of wide-necked intracranial aneurysms not amenable to coiling within the paraclinoid regions of the internal carotid artery. This is a particular matters meeting during which specific matters related to the PMA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act. A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Dr. David H. Mueller, M.S., is serving as Industry Representative, acting on behalf of all related industry, and he is employed by Mueller & Associates.

We would like to remind members and consultants that if the discussions involve any other products or firms not related to the agenda for which -- not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants needs to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the Panel of any

financial relationship that they may have with any firms at issue.

Appointment of Temporary Voting Status. Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27th, 1990, and as amended August 18th, 2006, I appoint the following individuals as voting members of the Neurological Devices Panel for the duration of this meeting on March 18th, 2011: Dr. Kyra Becker, Dr. Richard Byrne, Dr. Andrew Ku, Dr. Donald Richardson, Dr. Lynda Yang, Dr. Henry Brem, Dr. Peter Kang.

For the record, these individuals are special Government employees who have undergone the customary conflict of interest reviews and have reviewed the materials to be considered at this meeting.

This appointment was authorized by Jeffrey E. Shuren, M.D., J.D., Director for the Center for Devices and Radiological Health on March 8th, 2011.

Dr. Philip Posner has been appointed to serve as a Temporary Non-voting Patient Representative of the Neurological Devices Panel for the duration of the meeting on March 18th, 2011. For the record, Dr. Posner serves as a consultant to the Peripheral and Central Nervous System Drugs Advisory Committee in the Center for Drug Evaluation and Research. This special Government employee has undergone the customary conflict of interest review and has reviewed the material to be considered at this

session of the meeting. This appointment was authorized by Jill Hartzler Warner, J.D., Acting Associate Commissioner for Special Medical Programs, on March 14th, 2011.

Thank you.

Before I turn the meeting back to Dr. Hurst, I would like to make a few general announcements. Transcripts of today's meeting will be available from Free State Court Reporting, Inc., telephone 410-974-0947.

Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

The press contact for today is Karen Riley.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to the FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slide presentations to FDA, please arrange to do so with Ms. AnnMarie Williams at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and other electronic devices at this time.

Thank you very much.

Dr. Hurst?

DR. HURST: We'll now proceed to the Sponsor presentation from Chestnut Medical Technologies. I'd like to remind public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

The Sponsor will introduce the speakers. You have 75 minutes.

DR. CHER: Distinguished Panel members, esteemed colleagues at FDA, and to the public, good morning. My name is Daniel Cher. I'm head of Clinical and Regulatory Affairs at Chestnut Medical.

On behalf of the Chestnut team, I'm pleased to be here today to tell you about Pipeline Embolization Device. Pipeline is an investigational treatment for large and giant aneurysms. We believe that the data presented in our PMA, which we will summarize for you today, support a finding that the benefits of Pipeline outweigh its risks for the target patient population. We look forward to answering your questions today as you consider our data.

Dr. Aaron Berez, founder of Chestnut Medical, will present background information on aneurysms and, as well, describe Pipeline and the PITA study. I will describe the PUFS study, and Dr. Tibor Becske, the

PUFS principal investigator, will describe PUFS study results. Dr. Giuseppe Lanzino from Mayo Clinic will discuss the impact of Pipeline on the treatment of large and giant aneurysms. I will then return to discuss four additional items.

I'd like to now call Dr. Berez.

DR. BEREZ: Before we begin, I wanted to start with our indication statement. The Pipeline Embolization Device is indicated for the endovascular treatment of large or giant wide-necked intracranial aneurysms in the cavernous and paraclinoid regions of the internal carotid artery.

I would like to begin our presentation this morning with a bit of the background on aneurysm treatment and help you understand why we've created this new technology to treat patients with complex aneurysms.

Intracranial aneurysms are a balloon-like abnormality of the artery arising from a weakness in the arterial wall and are present in about 2 to 5% of the population. Each year in the U.S., about 27,000 people will have an aneurysm rupture. Forty-five percent of them will be dead within a month, and 1/3 of the survivors are left with a permanent disability.

Today we're going to focus on large and giant aneurysms that arise from the ICA. Large aneurysms are those with a maximum dimension of 10 to 25 millimeters, and giant aneurysms are those with a maximum

dimension of greater than 25 millimeters.

Large and giant aneurysms of the ICA are less common than smaller aneurysms, with only about 2,000 cases per year. However, they are more problematic. They are more likely to bleed, they're more likely to cause mass effect, and they're more difficult to treat.

Current treatment options today are varied. Direct surgical clipping can be an option, but it can be daunting. In a recent review of the single-center experience at UCSF in the surgical treatment of giant aneurysms, less than half were treated with direct clipping and the remainder required a surgical bypass.

Endovascular embolization with coils can be performed, but even with the advent of dedicated stents for the treatment of aneurysms, for example, Neuroform and Enterprise, not all patients can be treated, and complete aneurysm occlusion remains elusive.

Parent vessel occlusion, or sacrifice, is an option, but about a third of the people will require a bypass in addition because of insufficient collateral circulation. And in those patients who pass a balloon test occlusion and go on to have parent vessel sacrifice without a bypass, there's still about a 2 to 5% risk of permanent neurological deficit. In addition, many of these patients have bilateral aneurysms. And especially in those cases, doctors and patients prefer to maintain the patency of the parent vessel whenever possible.

Much of what we know about the history of unruptured aneurysms comes from the ISUIA study. ISUIA was a large, prospective and retrospective, multicenter study of unruptured aneurysms. Now, this wasn't a randomized study. As patients entered into ISUIA, they were assigned a treatment based on the preferences of their physicians. About 58% of the subjects were selected for treatment, whether that was surgery or endovascular treatment, and about 42% were selected for observation alone. These groups were followed in time for about four years.

First, let's look at the outcome for the patients that were simply observed. Patients with large and giant aneurysms of the ICA had a cumulative five-year rupture rate of 14.5 and 40%, respectively. As expected, the rupture rate was lower for cavernous aneurysms, reflecting their predominantly extradural location. The rupture rate for small aneurysms in this study -- it's not included on the slide -- was much lower, and this has created a lot of controversy in the neurosurgery community because it seems to be at odds with the daily practice of many neurosurgeons as well as previously published studies. But what's not controversial is the high rupture rates and the need for treatment for large and giant aneurysms.

In addition in this study, there's the possibility of selection bias because as they entered, close to 60% of the patients were selected for surgery or treatment right away, leaving the other 40% for observation. This

has raised the possibility that the patients that were selected for observation may have been at lower risk in the eyes of the treating physician, and thus, this cohort, when it's used to estimate the true natural history, may actually underestimate the rupture risk.

Now, let's turn to the outcome of the patients that were selected for surgery in the ISUIA study. This chart shows the likelihood of poor outcomes at one year in the patients who underwent surgery for anterior circulation artery aneurysms, that is, aneurysms that are similar to those that were in the PUFS study. Poor outcome in this study means moderate to severe disability, death, or impaired cognitive status.

If you were less than 50 years old, you had about a 4% chance of a poor outcome with a large aneurysm and about a 22% chance for a poor outcome with a giant aneurysm. And if you were greater than 50, the chance for a poor outcome with a large aneurysm increased to 25% and 33% for a giant aneurysm. Remember, this is elective surgery for unruptured aneurysms.

And what was the outcome for patients who received endovascular treatment in the ISUIA study? Well, the rates of poor outcome at one year were about 5 to 8% for large aneurysms and about 13 to 15% for giant aneurysms.

The treatment of aneurysms is essentially a treatment to repair the defect in the vessel wall at the neck of the aneurysm. Surgeons

do this with clips, and endovascular therapists do this by packing the aneurysm full of coils. The problem is, especially in large and giant aneurysms, the vessel wall defect can involve nearly an entire circumference of the vessel, as you can see on this 3D reconstruction of a patient that was in the PUFS study.

On the right-side of your screen is a cartoon drawing showing the vessel and the aneurysm in cross-section at the level of the aneurysm neck. You can pack this aneurysm with coils, but it's very difficult, if not impossible, to recreate the missing segment of vessel wall using coils. This leads to incompletely treated aneurysms that are only partially occluded.

One of the major issues with coil embolization of aneurysms and probably the major reason that the neurosurgery community has been slow to embrace it is that it often fails to provide a complete and durable aneurysm occlusion.

Let's look at Dr. Murayama's data from the UCLA experience in over 900 aneurysms published in 2003. Complete aneurysm occlusion in this study was tallied at the end of the procedure, and for patients with large aneurysms, 39% of them had complete occlusion. It was seen in about 28% of the patients with giant aneurysms. And these angiographic results were just reported by the investigators and were not independently adjudicated.

Complete aneurysm occlusion was the efficacy endpoint for the PUFS study, as we'll discuss in a few minutes. Why is complete

aneurysm occlusion important? Well, we know from the ISAT study that if you're left with a subtotal occlusion or neck remnant, your relative risk of retreatment is increased fourfold. And if your aneurysm was incompletely occluded, the relative risk for retreatment increased to sevenfold. Requiring prolonged periodic follow-up, these incompletely treated aneurysms can place a financial burden on the medical and a psychological burden on the patient. In addition, multiple radiographic studies for follow-up can result in a higher cumulative radiation exposure for the patient. And each additional retreatment session carries its own procedural risk.

We also know that ruptured aneurysms that are treated with coils but incompletely occluded leave the patient at risk of rerupture. In the CARAT study, the investigators found that the less the complete occlusion after treatment, the higher the risk of rerupture, which was increased nearly 22-fold for those aneurysms that were incompletely occluded. The authors concluded that the degree of aneurysm rupture -- or sorry -- the degree of aneurysm occlusion is a strong predictor of the risk of subsequent rupture and justifies attempts to completely occlude aneurysms.

Which brings us to the Pipeline Embolization Device. The Pipeline Embolization Device is designed to embolize an aneurysm through the endoluminal reconstruction of the parent vessel. And while my company has been developing this device since 2004, the fundamental work of looking at flow and its effect on aneurysms really began in the late 1980s. By the

1990s, there was experimental animal work that showed that stents alone could embolize an aneurysm. By the late '90s, there were case reports in the literature of stents being used as a treatment of pseudoaneurysms in the cervical carotid artery. And by the late '90s, there were reports of stent-supported coiling of intracranial aneurysms. Pipeline is really a natural evolution of this earlier work.

Here's a short animation that shows Pipeline placement. First, over a micro guidewire, a catheter is passed into the distal parent vessel. This is standard for many interventional neuroradiology procedures. The wire is removed, and the Pipeline device and its guidewire are inserted, and it's deployed through a combination of advancing the wire and retracting the catheter. The wire and catheter are removed, leaving the permanent implant across the neck of the aneurysm.

The Pipeline device works by two mechanisms of action. First, through flow disruption, and second, by providing a scaffold for endothelialization and repair of the defect in the vessel wall.

This video clip shows the Pipeline construct in the parent vessel and previously injected contrast pooling in the dependent portion of the aneurysm. Pipeline is disrupting the flow into and out of the aneurysm, leading to stasis in the aneurysm, which favors thrombosis of the aneurysm. This is a scanning electron micrograph from a vessel from an animal model that had been -- that had a surgically created aneurysm treated with the

Pipeline device.

This is an endoluminal view looking at the surface of the artery where the Pipeline had been placed and the aneurysm neck had previously been. The vessel is sliced open, and we're looking -- and what you see is a carpeted endothelium that's covered the Pipeline device. What you don't see is the aneurysm or the aneurysm neck or any filling of the aneurysm. The cut edge of the vessel, here circled in yellow, shows filaments of the Pipeline device embedded in the vessel wall. So the entire treated segment now of vessel is steel reinforced around its circumference.

With favorable results in the animal lab, we began our first human clinical trials in 2006 with the PITA study, conducted in Europe and South America. There were 31 subjects, all of whom had wide-necked aneurysms or aneurysms that had failed previous treatment. In this study, the use of coils was allowed with the Pipeline device.

At 180 days, complete aneurysm occlusion was seen in 28 out of 30, or 93% of the subjects. In the two subjects with incomplete occlusion, there had been previous treatment of the aneurysms with stents. Stroke was seen in two patients, for a rate of 6.5%.

The two-year data that you see on the screen is a recent update and has not yet been submitted to the FDA. In fact, it was not part of the study but is follow-up that's been obtained after the study was done. In reports that I've received from the investigators, all the 28 aneurysms that

were initially occluded are still occluded, and one additional aneurysm has gone on to complete occlusion, given a late complete occlusion rate of 96.7%.

The results from treatment of the aneurysms in the PITA study helped us as we prepared for our discussions with the FDA. This is an example from the PITA study, similar to a PUFS patient. This is a large paraophthalmic aneurysm seen in the AP view. On the 3D reconstruction in the upper left corner of the screen, you can see that at the level of the aneurysm, the parent vessel is really completely blown out. And, again, an aneurysm like this would be very difficult to treat with coils.

This aneurysm was treated with reconstruction of the parent vessel using the Pipeline device. This is the pre-treatment angiogram, and at six-month follow-up, the parent vessel has been reconstructed, and there's no longer filling of the aneurysm. In addition, the mass of the aneurysm, seen here on CT, extending up into the suprachiasmatic cistern, and you can see the calcified wall of the aneurysm here. At six-month follow-up, it was no longer present, with a nice CSF signal now adjacent to the Pipeline device in the suprachiasmatic cistern. This resolution of mass effect was mirrored in the early animal studies that we had done.

So what did we learn from PITA? We saw a high rate of angiographic cure, and this was independent of whether coils were used in conjunction with PED or not. There was a low rate of stroke, and we saw

improvement in mass effect in many patients. This information was helpful when we began discussing our U.S. IDE study, the PUFS study, with the FDA.

And now I'd like to ask Dr. Daniel Cher to return to the podium and discuss the PUFS study.

DR. CHER: PUFS is the pivotal trial that Chestnut submitted to FDA in support of PMA approval for the Pipeline device. PUFS is described in great detail in your Panel Pack, and we'll give the high points today. My job is to describe the PUFS study design and Dr. Tibor Becske will present PUFS study results.

PUFS is a prospective, multicenter, single-arm, interventional cohort. Each patient is followed for five years, but Chestnut and FDA agreed that the primary endpoint could be interpreted at 180 days. Ten centers are participating, eight in the U.S. and two outside of the U.S. And the target sample size is 100 patients.

To be included in PUFS, an adult patient had to have a single target aneurysm that was located in the intracranial portion of the internal carotid artery proximal to Pcom. The size had to be greater than 10 millimeters, that is, it had to be at least a large aneurysm, and the neck had to be greater than 4 millimeters. So I just want to emphasize here that we're looking at an aneurysm that's both large or giant and wide-necked. Please note also that there was no requirement regarding the shape of the aneurysm.

Patients were excluded from PUFS if they had undergone -- if they had had subarachnoid hemorrhage or major surgery in the past 60 days, if they had irreversible bleeding disorders, if more than one aneurysm required treatment in the next six months, if there was a stent in place, or if there was carotid stenosis. Please note again that there was no exclusion for prior treatment. That is, a patient could be included if he or she had had prior clipping, coil, embolization, or Onyx treatment but the aneurysm was still present. In addition, there was no exclusion for the shape of the aneurysm. That is, fusiform aneurysms were included.

As you know, PUFS is a single-arm clinical trial with a historical control. Chestnut and FDA thoroughly discussed options for concurrent controls. Both we and FDA agreed that we could not include coils or surgery as a concurrent control primarily because some large or giant aneurysms are not amenable to coils or are not amenable to surgery. Including such patients in the clinical trial would produce a bias against coils or surgery.

Similarly, stent-assisted coiling could not be used as a control because these devices are only available through the Humanitarian Device Exemption, or HDE route, wherein the Sponsor has to demonstrate safety and only probable benefit. Because of this, these devices could not be used as a control group.

As you heard from Dr. Berez, observation was also not feasible as a control group due to the high rate of stroke and death from rupture. In

addition, many of the patients had -- were highly symptomatic for their aneurysms, with severe headache or debilitating cranial neuropathy.

After substantial discussion with FDA, we agreed that a randomized trial was not possible, due to lack of clinical equipoise and due to known poor outcomes for the target patient population. We also agreed that there were adequate data in the literature to serve as a historical control.

And let me just summarize here, the goal of PUFS is not to show that Pipeline is better than coils or better than surgery. Rather, it's to show that -- it's to show safety and effectiveness in a group of patients with aneurysms that are either not amenable to coils or surgery or in whom outcomes are known to be suboptimal.

I want to point out that use of historical controls is consistent with FDA regulations. What I'm showing here is FDA regulations that state that historical controls can be used in diseases with high and predictable mortality or when it can be compared quantitatively with prior experience that's historically derived.

This slide shows the schedule of assessments. Patients were seen in the clinic at baseline, at the time of the procedure, at 30 days, 180 days, and again at one, three, and five years. Angiograms were performed at the time of the procedure, at 180 days, and again at one, three, and five years.

The primary effectiveness endpoint in PUFS was angiographic. To be called an effectiveness success, the 180-day angiogram had to show all of the following. First, there had to be complete occlusion of the target aneurysm. Then the target aneurysm was judged -- occlusion was judged according to the Scale of Roy, as shown at the bottom of the slide. Second, Pipeline had to be used alone without any alternative treatment. That is, adjunctive coiling was not allowed. Third, there had to be no major stenosis of the parent artery.

It's important to note that we took a very conservative approach to effectiveness assessment when interpreting aneurysm occlusion. Many published studies use terms like progressive thrombosis and stable aneurysm, terms which are vague, poorly defined, and highly subjective. As we showed earlier, when an aneurysm is incompletely occluded, there's an increased risk of retreatment and rebleeding. Therefore, our analysis used the core lab readings with a much more conservative approach, that is, whether the aneurysm was completely occluded or not. We think that this simple approach is clinically meaningful, helps with study interpretation, and sets a high bar for effectiveness.

I'd also like to point out that we took a conservative approach when counting successes. That is, if for any reason the patient was unavailable for a 180-day angiogram, we counted that patient as an effectiveness failure.

The primary safety endpoint to the study was the occurrence of major ipsilateral stroke or neurologic death, where major is defined as an increase of four or more points from baseline in NIH Stroke Scale. This is in contrast to most published studies, which don't prospectively define a safety outcome. In addition, we counted events towards the primary endpoint out to 180 days. And, again, this approach is different from what's typically reported in the medical literature, which is typically only perioperative outcomes.

The primary safety and effectiveness endpoints in the study were judged independently. The effectiveness was judged by a core radiology lab, consisting of three neuroradiologists who adjudicated all angiograms. Safety events were adjudicated by a clinical events committee, consisting of one neurosurgeon and two neuroradiologists, and they adjudicated all serious adverse events. They were not study investigators and had no financial conflict.

The historical control for PUFS was derived from a comprehensive literature review. Using Medline, we identified 1200 abstracts, and of those, 250 full-text articles that discussed the treatment of large and giant aneurysms. We submitted this information in the IDE for the PUFS clinical trial.

Together with FDA, we made the following conclusions. First, historical information was sufficient. Second, complete occlusion in these

large and giant aneurysms was uncommon, occurring less than 30% of the time. And, third, perioperative stroke and death were unfortunately common, occurring roughly 15 to 20% of the time. And these findings are consistent with that seen in the ISUIA study.

Taking this historical information into account, we proposed the following method for interpretation of the study. From the effectiveness perspective, the historical information showed us that complete occlusion of the target aneurysm at late time points was uncommon, occurring roughly less than 30% of the time. We therefore proposed to interpret PUFS as a success from the effectiveness perspective if we could show that the observed rate was statistically greater than 50%, as shown by the green line. And by statistically greater, I mean that the lower confidence limit of the observed rate, as shown by the green arrow, is greater than 50%.

We took a similar approach for the safety perspective. The safety information from the literature told us that the rate of stroke was roughly 15 to 20%. We therefore proposed to interpret PUFS as a success from the safety perspective if the observed rate of stroke was statistically less than 20%, as shown by the yellow line. And, again, by statistically less, I mean that the upper confidence limit, shown by the yellow arrow, was less than 20%

With the proposed sample size of 100 subjects, this study had adequate statistical power provided that the underlying but unknown

effectiveness rate was at least 70% and stroke and death rate was 7% or less, and these numbers were entirely consistent with what we had observed in the PITA study.

We took a Bayesian approach for interpretation of the primary endpoints. Bayesian approaches are commonly used, and they've been used in more than 20 PMAs, and there's an FDA guidance document on use of these approaches.

We calculated the probability that the effectiveness rate exceeded 50%, given trial data, and the probability that the safety rate was less than 20%, given trial data. We proposed to interpret the study as a success overall if we hit both of these endpoints. And the 0.975 probability value that you see there is analogous to a one-sided p-value of 0.025.

Secondary endpoints of the study are listed on the slide. First, complete occlusion of the target aneurysm at later time points. Second, the occurrence of major ipsilateral stroke, a component of the primary safety endpoint by 180 days. Third, change in Modified Rankin Scale at 180 days. Fourth, change in signs and symptoms related to the target aneurysm at 180 days. And, finally, the occurrence of device-related adverse events at 180 days and other time points.

This study had a number of additional endpoints, as shown on this slide. We won't have time to discuss all of them today, and Dr. Becske will present them as -- present highlights as he presents study results.

I'd now like to call up Dr. Becske to present PUFS study results.

DR. BECSKE: Good morning. My name is Tibor Becske, and I will be presenting the PUFS study results. I'm Assistant Professor of Neurology and Radiology at NYU where I work as an interventional neuroradiologist. I also hold a vascular neurology subspecialty, board certification, and I served as principal investigator for the trial.

By way of financial disclosure, I hold no stock in the Sponsor during enrollment phase of the trial. I have no financial conflict of interest. However, after the trial enrollment was complete, I have proctored a number of Pipeline cases outside of the United States in countries where the device has already been approved. And I have received compensation for those services. My travel and lodging to be here today are also reimbursed by the Sponsor.

First, I would like to start by thanking my co-investigators, 27 of them, from the United States, Turkey, and Hungary for participating in the trial. I would also like to thank the referring physicians from throughout the United States for referring patients to be treated in PUFS. As you can see, eight sites in the United States enrolled 70% of the patients with the remaining 30% being enrolled between a center in Turkey and one center in Hungary.

Despite the geographical diversity of the enrolling sites, the data were determined to be poolable based on the following considerations.

The same protocol was used or the same CRFs at all sites. The study implementation and monitoring was the same at all sites. There were no significant differences observed in baseline characteristics or primary safety and effectiveness endpoints in the trial across sites.

Patients in Pipeline -- I mean in PUFS study were similar to patients in other aneurysm trials. You can see nearly 9 out of 10 patients were women. This is not surprising, given that it is known that aneurysms are more frequent, more common, in women. As you recall, PITA had also a similarly large majority of women subjects. Eight patients failed prior attempts of treatment of their target aneurysm, mostly by coil embolization.

PUFS was a trial of large and giant aneurysms. This slide shows the mean size of the aneurysms was 18.2 millimeters, and the mean neck size was 8.8 millimeters. There was one patient that was enrolled with a less than 10-millimeter sized aneurysm. However, this aneurysm was excluded from primary effectiveness analysis even though it met primary success criteria.

This slide shows anatomic distribution of the treated aneurysms along the internal carotid artery. The most common locations were cavernous and paraophthalmic, but you can see that aneurysms in all pre-defined target locations were treated.

Procedure time was averaging around two hours, with mean fluoroscopy time around 50 minutes. You can see a wide range, as some

aneurysms were very complex, and prolonged procedure times were typically due to the difficulty in gaining access to the distal parent vessel.

On average, 3.1 devices were used to treat an aneurysm, with 79% of the patients treated with two or three devices.

You saw in your Panel Pack that the FDA has asked you to consider potential issues related to total fluoroscopy times required for the use of Pipeline. This was prompted by two instances of observed alopecia, one in PITA and one in PUFS. We would like to offer this information for your consideration of this question.

The mean fluoroscopy time in PUFS was 48 minutes, as shown by the light blue shading on the top of the table. The dark blue shading shows fluoro times from three recent studies where aneurysms were treated with coil embolization. As you can see, mean fluoro times were one hour or greater. The last two studies here do not discuss specifically the size of aneurysms treated. However, in reading the articles, it is unlikely that they treated more than a handful of large and giant aneurysms. So, in summary, there is no evidence that the fluoroscopy time is longer in Pipeline treatment as compared to aneurysm treatment of similar-sized aneurysms.

Pipeline placement was highly successful. Of the 357 devices that were placed in a microcatheter, 349 or 97.8% were delivered successfully. Eight had to be removed before reaching a patient for various reasons -- before reaching the target location for various reasons. Five of

them were related to excessive friction within the microcatheter -- between the device and the microcatheter. And all these cases were then successfully completed using other Pipeline devices. There was one delivery wire breakage in a very complex case after the deployment of the last stent.

Study follow-up was excellent. You can see that of the 104 patients that were theoretically available for follow-up at the primary safety and effectiveness assessment at 180 days, 100 did undergo clinical and angiographic follow-up. The other four subjects had been in contact with the investigators, however, refused full follow-up.

Let's now turn to effectiveness analysis. As you recall, the primary effectiveness endpoint was defined as complete occlusion of the target aneurysm at 180 days without major vessel stenosis. In the primary analysis, we observed 78 successes for a rate of 73.6%. The probability that the study met its predetermined endpoint, shown here shaded in green, was over -- greater than 0.9999. Although the primary analysis was Bayesian, the frequentist p-value compared to a rate of 50% was found to be highly statistically significant, at less than 0.0001.

This slide shows a sensitivity analysis similar to the one that the FDA has shown you in its Executive Summary. The first row displays the analysis that I just showed you. In the second analysis, we exclude two patients whose contralateral aneurysms were treated. In the third analysis, all patients with all treatment attempts were accounted for, including for

subjects who are either ineligible based on their aneurysm size or location, and also including one patient of the total four whose catheterization attempt failed and so no Pipeline attempt was made -- placement attempt was made. Finally, the fourth analysis shows the way the literature would typically be reporting, that is, simply by omitting from the denominator the patients with no follow-up information.

As you can see, no matter how you do the analysis, the results are very similar, with a very high probability that the trial met its effectiveness threshold and very low frequentist p-values. I would like to point out that while the first analysis in this table was submitted to the FDA, the other three at the bottom were not yet submitted to the FDA.

Next, I would like to show you a few cases from the trial. This first patient presented with prominent eye symptoms and headache related to this giant cavernous segment aneurysm. Under three, the image at the top left corner, you can see how the aneurysm neck is very wide and the vessel is nearly circumferentially involved. On the lateral pre-treatment angiogram, you can see the aneurysm, and the six-month follow-up on the right side demonstrates complete occlusion of the aneurysm with very nice remodeling of the parent vessel reconstruction. No residual aneurysm filling and no stenosis was observed. Her symptoms improved significantly.

This next patient is very similar. Again, a giant aneurysm, wide-based, nearly circumferential involvement of the vessel wall, and nice

reconstruction at six months without significant stenosis.

This is a woman with an asymptomatic large supraclinoid aneurysm that was treated. And as you can see, at six months, on the right-hand side image, there's a nice reconstruction of the parent vessel without any evidence of residual aneurysm filling or stenosis.

I would like to remind the Panel that our core laboratory used a very conservative approach in determining success. Any amount of contrast filling within the aneurysm at six months, such as shown here, was called a failure for primary effectiveness analysis. If coil treatment of this aneurysm had been feasible, this amount of contrast may or may not have been demonstrated on a follow-up angiogram due to the radial opacity of the overlying coils. And so had this aneurysm been coiled, it would have most likely been called a complete success. In our trial, this is a failure.

Let's now turn to primary safety analysis. The primary safety endpoints were defined as major ipsilateral stroke or neurologic death at 180 days. We observed six events that met these criterion for a rate of 5.6%. So we found that the posterior probability that the observed event rate was below the predetermined 20% threshold was greater than 0.9999, with an analogous p-value, as shown here, both highly statistically significant.

Of the six primary safety endpoint events, two were thrombosis -- parent artery thrombosis with resulting stroke, one was

stenosis with a stroke, two were intracranial non-subarachnoid hemorrhages, and one unclear death that was interpreted as a possible neurologic death, for a total of six events.

The study also had four predefined subgroups for both safety and effectiveness. And as you can see from this table, looking at effectiveness, none of these made a difference for Pipeline with respect to its ability to completely occlude the target aneurysm.

A similar analysis for subgroups for safety was also done with similar results. So we concluded that these subgroup analyses yielded little evidence to support a difference in safety and effectiveness across the subgroups.

Let's now turn to secondary endpoint. The first secondary endpoint was aneurysm occlusion over time. This table shows occlusion rates at 180 days and at one year amongst subjects who underwent angiograms at each time point. Just the chart considers aneurysm occlusion only. That is, it doesn't consider the presence of stenosis.

At six months, you can see the observed rate was 82%, with the same number at one year at 86%. And this was related to five aneurysms that have progressed from residual filling at six months to complete occlusion at one year and one patient that refused the angiogram at six months who had complete occlusion at one year. From this, we conclude that there was a durability effect of Pipeline out to one year.

Additional secondary endpoints included major ipsilateral stroke at 180 days, for a rate of 5.6%, as discussed earlier. We also looked at change in MRS scores, Modified Rankin Scores, at 180 days, as compared to baseline. In this analysis, you can see that close to 90% of the patients were within one point of baseline with a small number of patients showing improvement or worsening by two or more points.

The fourth secondary endpoint was any change in pre-existing aneurysm-related neurologic signs and symptoms. Of 76 subjects who had signs and symptoms related to their aneurysms, target aneurysms, at 180 days, 51% were found to be improved, 25% were unchanged, and 11% were worse. We saw many patients whose neurologic deficits improved and whose headaches resolved. So we conclude that there was a substantial positive effect of Pipeline in a number of patients.

The last secondary endpoint is the occurrence of device-related adverse events at 180 days. Of a total of 21 events, 15 were rated as probably related to the device, with six rated as definitely related to the device, the most common ones being headaches in seven instances, amaurosis fugax in five, and ischemic stroke. Please note that none of the seven headaches represented stroke or hemorrhage. They were thought to be symptomatic of the evolving clot within the aneurysm, target aneurysm.

As Dr. Cher mentioned, there were several additional endpoints in PUFS, the details of which are in your Panel Pack. All of the

additional endpoints were supportive of safety and effectiveness. Here are some highlights. There were no secondary procedures, defined as additional procedures, to address symptomatic progression after Pipeline placement. There were no instances of Pipeline migration. And over 50% stenosis was observed in two subjects, for 1.9%.

Finally, before we end, let me cover adverse events. There were 44 events that met the trial's definition of serious adverse event. Note that the international standard was used to define serious adverse events. That included rehospitalization or prolongation of existing hospitalization for any reason. And as such, it goes beyond what is typically reported in the literature with aneurysm treatments. Of the 44 events, 25 were neurologic and 19 non-neurologic. The 25 neurologic events were observed in 22 subjects. The most common serious adverse events were amaurosis, headache, and intracranial hemorrhage. Again, I would like to point out that a patient with headache counted as a serious adverse event if their existing hospitalization was prolonged or if they had to be rehospitalized for management of the headache. None of the patients with amaurosis progressed to complete visual loss.

Of the 19 non-neurologic serious adverse events, in 13 subjects, the most common was non-neurologic bleeding in five cases. Many of these events were completely unrelated to the subject's underlying aneurysm, and none were found to be related to the Pipeline device.

To summarize the results briefly, Pipeline was found to be highly effective, with a 70% complete aneurysm occlusion rate, which was highly statistically significant compared to the 50% target. The Pipeline had a reasonable safety profile, with a 5.6% rate of events, meeting the primary study endpoint. The trial met its predefined endpoint of less than 20% with a high degree of statistical significance. Pipeline performance was found to be excellent, with a high rate of deliverability and accurate placement. And, finally, the follow-up of the trial was excellent, with 96% follow-up rate.

With that, I would like to invite Dr. Lanzino to give his presentation.

DR. LANZINO: Thank you. Good morning. Giuseppe Lanzino. I'm a Professor of Neurosurgery and Radiology at the Mayo Clinic in Rochester. I'm a neurosurgeon with dual subspecialty training in endovascular procedures and open cerebrovascular surgery. These are my disclosures.

I'd like to briefly put in perspective the problem of large and giant intracranial aneurysms because there is a unmet medical need for these aneurysms. The issue relates to the risk of rupture. And we know from the ISUIA study that the risk of rupture is substantial. I'd like also to stress that the ISUIA study was not a population-based observational study. It was a study cohort, a different treated and untreated cohort, where the treatment decision was made by the physician, and therefore the rates of

bleeding are probably higher than what ISUIA had suggested, as the majority of patients failed to be at risk of rupture were indeed treated.

For these specific aneurysms in the paraclinoid area, there are issues related to mass effect and symptoms related to mass effect that are disabling, related to double-vision, facial pain, and progressive optic neuropathy. The treatments that we have available are far from ideal. Surgical treatment is effective, but definitely quite invasive and very technically challenging. And it's becoming more and more challenging nowadays as there are only a handful of surgeons experienced with the treatment of these lesions because the majority are being treated with endovascular treatment.

Endovascular treatment in itself is becoming safer and safer, but for these aneurysms, it's definitely incomplete. There is a need for prolonged monitoring. There is a very high incidence of residual aneurysms and recurrences that creates a lot of anxiety with patients, families -- need for retreatment and need for prolonged monitoring.

So the introduction of the Pipeline endovascular device, as we stressed before, is the combination of a long journey that started more than 20 years ago. And it was originally based on pure in vitro study and flow dynamics at the time, where only a handful of labs were interested in computation of fluid analysis. And then it was translated into early animal studies and then earlier clinical series, as we have heard. Now, we have

some fairly good clinical trials and also a few single-center series.

The PUFS study is not a randomized study. It would have been very difficult, actually impossible to design a randomized trial with this particular patient population. We do not have a standardized or valid alternative that we could consider equally safe. And, also, the treatments available have not been submitted to rigid scientific scrutiny. And most of the information we have, as we have heard, it's based on single-center experiences. And, therefore, the complication rates in real life are probably higher than what the single series have indicated.

There are several strengths of the PUFS study, I think. It's a prospective and multicenter study. There are fairly well-defined endpoints. The report forms and the examinations were standardized. It was consecutive enrollment, close monitoring of the study data. There is a very high rate of follow-up adherence. If we look at most of the modern and even single-center endovascular series, if we get a angiographic follow-up of about 75% at six months, it's a very high rate. In the PUFS study, as we have heard, there was far greater than 90%.

The definition of treatment success was fairly clearly defined as unlike the other endovascular series, where there are different grades of occlusion in the PUFS study. The effectiveness was clearly defined as total occlusion or incomplete occlusion, with incomplete occlusion being considered a treatment failure. There was independent adjudication of

effectiveness by core lab, and we'll see why this is very important in an endovascular study. Strokes were clearly defined. And, also, unlike many other studies, where we usually tend to focus on the periprocedural, perioperative complication rate within 30 days, there was a very long and conservative time allowed for the definition of periprocedural strokes.

The importance of the core lab before a study of this type is stressed by an analysis that was done for another study, where there was a comparison between the degree of complete occlusion as assessed by the operator doing the treatment versus the core lab. And as you can see, the core lab was much less likely to define a complete occlusion, 44%, while when it was left to the operator assessment, it was reported as 61.5%. And the same effect was seen in the definition of residual aneurysm remnant. It was 1/3 by core lab assessment and 5.3% when it was left to the discretion of the operator. And this was part of a multicenter prospective trial as well.

So is the PUFS study successful? Well, these are aneurysms -- the aneurysms treated -- as we have heard, are fairly challenging aneurysms. They are often not only very large or giant, but they have fusiform configuration and they have a wide neck, which makes both surgical and endovascular treatment quite challenging. Some patients had already failed what we would have considered standard current traditional treatment.

One of the exciting features of these type of devices is the ability to completely obliterate the aneurysm without even heading to go

into the aneurysm because the device is placed across the neck of the aneurysm. And in the PUFS study, the degree of complete occlusion was 75% at six months, again, using a fairly conservative criterion that we'll show some cases that were considered incompletely occluded, where most of us would consider the treatment actually a success.

And the data also suggests that for the subset of aneurysms enrolled in this trial, paraclinoid aneurysms involving the internal carotid artery proximal to the take-off the posterior communicating artery, there was a good degree of safety.

This is actually one of the first patients that was treated at our center. This patient, interestingly enough, was referred by the surgeon who had pioneered the use of long saphenous vein bypass for the treatment of giant and large internal carotid artery aneurysms. This patient presented with intermittent double vision and ophthalmoparesis. And you can see the fusiform morphology of the aneurysm on the left. At the center is the six-month follow-up angiogram that shows greater than 95% obliteration of the aneurysm with a very small persistent neck that underwent complete obliteration at one year. So the ability to completely obliterate these aneurysms with an endovascular device without the need of actually invasive catheterization of the aneurysm itself represents a major shift in our endovascular ability to treat these aneurysms.

This is another quite challenging case, a very irregular tri-lobed

aneurysm of the paraclinoid carotid artery. Again, at six month, a result that most of us would consider really an excellent result, but there is a residual aneurysm filling. And then at one year, there is a very small residual aneurysm right at the take-off of the ophthalmic artery. So a result that is excellent from a clinical and radiological point of view, although with a very conservative reporting approach, it's still considered a treatment failure in a way.

And, again, this is another case. And after a while, you can see, it becomes quite bothering to see these pre and post pictures with these dramatic results, but it's exciting for the ones of us that have really followed this evolution, knowing the frustrations we have gone through in the treatment of these aneurysms, to be able to see with certain consistency these type of results.

Again, the traditional and current endovascular treatment of some of these aneurysm with the coils, with or without assisting device like balloons or stenting, is associated with a very high incidence of residual and recurrent aneurysms and with the underlying risk of further aneurysm growth and recanalization.

One of the main features of this device is it actually works quite well in patients who have failed previous treatment. And this is a patient that had undergone coiling of the aneurysm with an originally fairly good result, but you can see the problem after six months, there is a

recurrence with partial filling of the base of the aneurysm, and after placement of a Pipeline device, there is a complete remodeling of the parent vessel and obliteration of the part of the aneurysm that is still filling.

When we deal with endovascular devices, we are worried about the risk of delayed parent artery occlusion or stenosis. And so far, the profile demonstrated by this device for the particular type of aneurysms that we are considering today has been extremely favorable, with a very low rate of stenosis and -- as compared even to traditional intracranial stents, where the reported degree of stenosis is higher than what we have seen in the PUFS study.

So I think that for -- from the data that we have in this subset of aneurysms, it seems that the benefits of the Pipeline endovascular device do outweigh the risks. There is a very high rate of complete aneurysm obliteration in a very difficult subset of aneurysm to treat. The incidence of periprocedural -- at six months complications -- significant complication rates is acceptable given the nature of these aneurysms and given also the fairly high morbidity of current alternative treatment.

We do see local effects. The main mechanism of the device is the arrangement of flow and the induction of a thrombosis within the aneurysm, so it is fairly common that these patients within the first two weeks after treatment do develop some degree of headache which responds quite favorably to steroid treatment, and that tends to resolve

spontaneously.

Patients who have already cranial neuropathy from mass effect from the aneurysm can undergo transient deterioration of their symptoms, but what we have seen, overall, there was a 50% rate of improvement of pre-existing cranial neuropathy, which compares favorably with the degree of improvement which we see with the more traditional means, which is usually in the rate of about 30%.

And there are, in addition to the PUF data, there are several patients that have been treated in the United States under compassionate use. There are other series in Canada, single-center series in South America, and large experience in Europe, which suggests that for this subset of aneurysm involving the internal carotid artery proximal to the take-off of the posterior communicating artery, this is an effective and safe treatment.

Thank you.

DR. CHER: As we close, I'd like to address four additional items that are shown on this slide. We have ten minutes, so I may not be able to get to all of the items.

Pipeline is currently commercially available in 52 countries across the world. It's relevant, therefore, to review the safety experience in those 52 countries. Pipeline was launched in Europe in September 2009, and other countries followed soon thereafter. Because of our training program, we're in close contact with the OUS practitioners, and although

there are no ongoing formal studies, the close contact that the company has provides a high degree of assurance that most of the serious adverse events are captured.

This slide shows information that we have not previously presented to FDA and has been obtained recently. Between September 2009 and January 2011, approximately 3400 devices have been provided to physicians in other areas of the world, and we estimate that approximately 1600 patients have been treated. The table shows the number and estimated rate of hemorrhagic, ischemic, and other events. Although these are data that are not from a study, the data provide some reassurance that the observed rates in the commercial setting do not appear to be different than those that we've reported in the IDE.

I'd like to address how we're going to maximize safety in the post-approval setting with the following three items. We've proposed a training and marketing plan, as shown here. Physicians will attend a one-day centralized multidisciplinary course in which there will be didactics as well as use of a benchtop model, the same benchtop model that we used to train physicians in the clinical trial. We've received excellent feedback regarding the benchtop model, and it's really quite challenging and very useful.

Physicians' first five, at least the first five cases, will be proctored by a physician with experience, and there will be continued support by company personnel after those first five cases. We are planning

a controlled market release of this product, training roughly 30 to 50 sites annually.

I'd like to turn next to post-approval study. FDA has asked you some questions about a post-approval study, and it's described in your Panel Pack, but I'd like to give you some details. FDA's main concern in discussing the post-approval study was long-term safety. As you know, PUFS is a five-year study. And when we designed PUFS, we agreed with FDA that much of PUFS could be done in the post-approval setting. We have therefore decided to change our focus to look at all ipsilateral strokes. Therefore, the primary endpoint of the post-approval study is the occurrence of any stroke or neurovascular death at five years.

We have performed power calculations using computer simulations. In these power calculations, we've modeled the ten strokes that have already occurred to date. We've assumed about a 1% yearly rate of stroke in the long term. We've also assumed loss to follow-up, as you see here. The goal of the study is to show that the cumulative rate of stroke or neurovascular death is statistically less than 25%.

And this slide shows how those calculations work. The yellow line represents the occurrence of ten strokes that have occurred to date. The *x*-axis is time; the *y*-axis is the cumulative chance of stroke. We've modeled approximately a 1 to 2% rate of stroke in the long term in follow-up, and our goal is to show that the cumulative rate of stroke is less than

25%, statistically less than 25%, by which I mean that the upper confidence limit, as shown here in the yellow arrow, is less than 25%.

Power calculations have shown that there is adequate power to the post-approval study provided that the underlying yearly rate is less than about 2.1%.

FDA has asked you a number of questions, and I'd like to give you our perspective on these questions. FDA has asked you whether a modification to the indication statement is warranted regarding the youngest appropriate age. I wanted to let you know that we are not requesting a pediatric indication. However, it may be appropriate to add a precaution along the lines of safety and effectiveness has not been evaluated in the pediatric population.

You have been asked whether the indication statement needs modification regarding a contraindication for ruptured or unruptured -- I'm sorry -- a contraindication for ruptured aneurysms. The instructions for use already contain a contraindication for patients in whom dual antiplatelet therapy is contraindicated. However, it may be reasonable to add a contraindication in the setting of acute subarachnoid hemorrhage.

FDA has asked you to consider the wording that we've proposed for the anatomic location that was treated in PUFS. We've also had discussions with FDA, and we've proposed an additional or an alternative indication statement that substitutes the term paraophthalmic

for paraclinoid. This was based on feedback from some of the physicians that we spoke with.

FDA has also asked you about whether the label should include warnings or precautions regarding the use of ancillary devices such as angioplasty balloons or coils. The protocol allowed use of ancillary devices. And as you saw, coils were used in one case to help access the distal parent vessel. The case report forms in PUFS did not include -- included a collection of, use of ancillary devices, but not why they were used. We subsequently queried sites for why balloons were used. The most common cause, as you see written here, was narrowing from mass effect. In two cases they were used for access techniques prior to use of Pipeline. In two cases they were used to fully appose the Pipeline to the vessel wall after deployment. And in five cases, they were used to fully open the device.

Based on this info, we believe it may be appropriate to add to the instructions for use: When using ancillary devices during Pipeline placement, refer to the commercial labeling for use of those devices. The reason is that we saw no unique risks associated with use of these ancillary devices, and therefore, no additional warnings or precautions are needed beyond those that are already present in the ancillary device labeling.

Finally, before we end our presentation, I'd like to review FDA's definitions of three terms that are key to your deliberation regarding FDA's discussion questions 7 through 9. FDA requires that safety and

effectiveness be supported by valid scientific evidence. FDA defines valid scientific evidence as that coming from a variety of sources, including studies and objective trials without matched controls. This includes well-conducted single-arm studies like PUFS.

FDA defines reasonable assurance for safety when there is valid scientific evidence that the benefits outweigh the risks. You've heard from Drs. Becske and Lanzino how the benefits of Pipeline for the target patient population outweigh its risks.

FDA defines reasonable assurance for effectiveness as occurring when a significant portion of the target population has clinically significant results. We've seen that the effectiveness success in PUFS was very high for this difficult to treat patient population and therefore represents clinically significant results.

In closing, we have developed Pipeline for a critical unmet need, large and giant intracranial aneurysms. The data we have brought meet FDA's requirements for PMA approval in that they provide evidence that the benefits outweigh the risks for the target population, the trials provide valid scientific evidence, and they meet the standard for reasonable assurance of safety and effectiveness.

We look forward to answering any questions about PUFS and Pipeline. Thank you for your time.

DR. HURST: Thank you. I'd like to thank the Sponsor's

representatives for their presentation. Does anyone on the Panel have a brief clarifying question for the Sponsor? Please also remember that the Panel may also ask the Sponsor questions during the Panel deliberations this afternoon. And please remember to state your name before speaking.

Dr. Eydelman?

DR. EYDELMAN: Prior to that, I just wanted to point out one more time that the information presented on slides 11, 28, 42, and 47 contained information not previously submitted to or reviewed by the FDA. Thank you.

DR. HURST: Thank you, Dr. Eydelman.

Yes, Dr. Yang?

DR. YANG: I found the adverse event profile very good, but I have a couple of clarification questions. One of them is that you mentioned in the Panel Pack that there are six subjects in whom delivery of one PED was unsuccessful, but 50% of those had serious adverse events within days of the procedure. Can you give us some details on what those were?

DR. CHER: I can, and I can present that to you after the break. I will find those slides and bring them up.

DR. YANG: Okay. And then the second question I had was you indicated 80% of the patients had more than one device inserted and a few that had four or five devices inserted. When you looked at the adverse events, again, for that -- although you looked at them by different aneurysm

type, and all that -- did you see any increase in adverse events with the increasing number of devices, and is there a top line at which you should stop?

DR. CHER: We did examine the relationship between the number of devices used and the occurrence of the primary safety endpoint, and we saw no statistical relationship.

DR. YANG: Either early or at 180 days?

DR. CHER: That's correct.

DR. HURST: Dr. Ku?

DR. KU: I have a couple of questions. On your slide number 53, you indicated that balloon use was used to address narrowing from mass effect. Now, does that really refer to incomplete expansion of the stent or mass effect from the aneurysm since, theoretically, there should be no mass effect because it's still liquid within the aneurysm.

DR. CHER: Probably the best thing to do is to bring up some examples, and we'll try to find those slides for you. We saw many cases in which the large and giant aneurysm -- understand that these aneurysms are in a confined space, and when the aneurysm becomes larger and larger, it pancakes or pushes on the parent artery, and also -- pardon me. Let's try to find case pictures.

In addition, the arteries themselves are dysplastic, and whatever it is that's causing the artery to become aneurysmal in one place in

many circumstances caused -- that's a good example. Can we bring this one up?

Here's an example of the kind of stenosis that we saw. This is a patient referred from Atlanta to New York for treatment of a giant aneurysm. You can see that the aneurysm itself displaces the parent artery and causes flattening and narrowing of the parent artery. We saw this in several cases, as you noted. In many cases, the physician wanted to treat the underlying stenosis as well as treating the aneurysm. And, you know, these two disease processes occurred at the same time. And, therefore, the Pipeline was placed, immediately after which a balloon was used inside of the Pipeline to try to treat the underlying stenosis.

DR. KU: Okay. So it really refers to underlying stenosis, not --

DR. CHER: Yeah, let me show you one more picture as well. Here are examples of post-aneurysm stenosis in this particular patient. There's another slide that's one or two later, if you can bring it up, that has some more good examples. This slide. This is the one I was looking for. Let's bring this one up.

So you can see, I've noted with the arrows that there are places where there's really severe narrowing of the parent artery where the aneurysm is located. I don't know what this due to, but I think it's because the aneurysm is expanding in a location where there's not a lot of room to expand, and as well, the arteries themselves, the underlying arteries

themselves are dysplastic.

Dr. Becske, did you want to say anything more, or Lanzino?

DR. BECSKE: Yes. I'm Tibor Becske. Yes. I just wanted to say that these were underlying narrowings not thought to be related to atheromatous disease, and we found they were related to mass effect of the aneurysm itself.

DR. CHER: And we often saw that the 180-day angiogram actually looked better and the stenosis got better.

DR. KU: Okay. Now, when you needed to do the angioplasty, I noticed that there was one patient with a history of CC fistula developing. With the balloon angioplasties, were you using compliant or non-compliant devices, and what degree of inflation and pressure did you need to get a so-called angiographically more appealing appearance?

DR. CHER: Yeah, I believe -- I didn't -- I was having a hard time hearing what you were saying at the end.

DR. KU: Were you using either compliant or non-compliant angioplasty balloons and -- in order to get a more appropriate angiographic occurrence for those areas of stenosis. And, also, what types of pressures were you using if it was a non-compliant balloon because that would theoretically be a somewhat risky procedure even though, as you guys have said that it's not atherosclerotic, but obviously, it's not defined or path-proven as non-atherosclerotic. It could be fibrotic reaction, you know, of

the vessel in relationship to the aneurysm. I mean, there are many possibilities.

DR. CHER: Yeah. I can tell you what I know about the case. This was at the very end of the case, and the physician placed the balloon actually outside of the -- just proximal to the placement of Pipeline. I believe it was a Gateway balloon, and I do not have information on the pressures that were used. It did cause a carotid cavernous fistula and a small subarachnoid hemorrhage, which resolved shortly -- actually, two additional Pipelines were placed over the carotid cavernous fistula, and a few days later, it was gone.

DR. BECSKE: Tibor Becske again. If I may, I would like to point out that in several instances, the angioplasty was done prior to the placement of the devices. A variety of balloons were used, and that was based on physician preference. Some were compliant, some were non-compliant, and we didn't record the pressure parameters that were required in the non-compliant balloons.

DR. KU: Okay. Now, these stents, I assume, are non-self-expanding, is that correct, or are they self-expanding?

DR. CHER: They're self-expanding.

DR. KU: Okay. Now, is there any consideration with the angioplasty pre-stent placement for these areas of stenosis because, obviously, intracranial angioplasty is a non-trivial procedure and can be

associated with significant morbidity and mortality?

DR. CHER: In general, the number of patients that we saw who had pre- or post-aneurysmal stenosis was small. And from our perspective, you know, this is treatment of a disease that we're not aiming to treat, and we don't make the devices to treat that disease. So I think that the risk profiles really are associated with the use of the balloons for this type of procedure and not necessarily with Pipeline.

DR. KU: So it's really physician decision as to whether or not to angioplasty? Because theoretically, with self-expanding stents, there are many cases where even though there's a stenosis, once you place the device with a delayed follow-up, the self-expansion will dilate the vessel without requiring a high degree of pressure.

Okay. Couple more questions. You had a number of patients, let's see, table 8, where you indicated that -- baseline characteristics of the patients. You had, I believe, 70-something patients, let's see, with follow-up on -- or with pre-existing cranial neuropathy --

UNIDENTIFIED SPEAKER: Excuse me. What slide number was that, Dr. Ku?

DR. KU: Oh, it wasn't a slide number. It was on their -- oh, I'm sorry. I'm looking in the wrong source. That's it for now.

DR. BECSKE: Can I please go back to the previous question? I just would like to make an additional comment, and that is -- I am just

speaking for our own center at NYU. So in no case did we plan to do an angioplasty. And that was based on the fact that most of these patients were referred from out-of-state and we had a limited number of angiographic images. So in most of the cases, we were unaware of the compression of the parent vessel at any location. And so as the patient was on the table and we found -- we felt it was in the patient's best interest to continue and complete the procedure even though, yes, we did realize there's a potential for slightly increased safety events occurrence.

DR. HURST: Dr. Byrne?

DR. BYRNE: The ischemic strokes that you saw, were the majority of them embolic or were they from perforators, or what was the experience there? I assume embolic.

DR. CHER: One of the ischemic strokes was due to thrombosis of the parent artery occurring the night after Pipeline placement. One of the ischemic strokes was due to a patient who went home -- oh, slide up, thank you -- the next patient is the first one in this row. This is a patient who went home. Her husband died around postoperative day 30. She refused follow-up. A physician from NYU graciously got on a plane and went out to northern Wisconsin to visit her and noticed that there was evidence of medication non-compliance. She refused 180-day angiogram. She eventually had a CT angiogram at around ten months, which showed thrombosis of the parent artery, and that was associated with stroke.

The patient on the second row had a very large, very complex -- it was a giant, complex aneurysm that had -- she had perfect reconstruction of the artery at six months. She saw a physician for a brief neurologic episode, and MR was consistent with a lacunar stroke. Whether that's embolic in origin I can't really say.

Maybe you can help me describe these carefully?

And then the fourth one was a woman who, at postoperative day 62, had stenosis of the parent artery causing stroke.

DR. BYRNE: How about minor stroke? How about radiographic findings consistent with minor stroke?

DR. CHER: We did not include any routine postoperative imaging, so I don't have data on those. No routine postoperative cross-sectional imaging. It was all --

DR. BYRNE: So there wasn't --

DR. CHER: It was angiogram --

DR. BYRNE: -- routine CT scan after the procedure?

DR. CHER: Whether the physicians needed to do a CT scan was left to the discretion of the physician. That was not included in the study protocol.

DR. BYRNE: How long were patients kept on aspirin and Plavix?

DR. CHER: The clinical protocol required that patients take

aspirin, 325 milligrams, for two days prior to the procedure and at least six months after the procedure, after which use of aspirin was at the discretion of the physician. For clopidogrel, the protocol required 75 milligrams for seven days prior to the procedure and for at least three months after the procedure, after which use was at the discretion of the physician.

DR. BYRNE: And what is their discretion, typically? Do they keep them on it and for how long?

DR. CHER: Many patients were kept on aspirin. I believe at one year -- I can try to find the data for you -- but I believe that most patients were off clopidogrel and roughly 2/3 of patients were still on aspirin.

DR. BECSKE: If I may, going back to the previous question, that one lacunar stroke in the table was from an MCA perforator, and it was not from a covered segment, stent-covered segment of the vasculature.

DR. HURST: Dr. Evans?

DR. EVANS: Scott Evans. Very nice presentation. Could you just elaborate a bit more on -- it seems like my mike is -- could you just -- hello? Maybe it's just me.

(Laughter.)

DR. CHER: I can hear you.

DR. EVANS: Could you just elaborate a bit more on the selection of at least a 50% effectiveness rate and at most a 20% safety event

rate as your goals for the study?

DR. CHER: Right. So at the beginning of the study we conducted a thorough literature review. We identified in the literature review, attempted to identify studies that reported clinical outcomes of patients who had undergone either coil embolization or surgery for large or giant aneurysms. We identified a large number of articles, many of which described patients with smaller aneurysms of which there were a handful with larger and giant. We carefully abstracted information from 250 full-text articles that looked to be relevant.

The information was submitted in tabular format to FDA. In discussing with FDA, we agreed that the information was not reported in enough detail to do any quantitative analysis. However, from a qualitative basis, we saw that complete occlusion of the aneurysm, when it was reported, when late complete occlusion was reported as a study outcome, it was very rare, less than 30% of the time in patients with large and giant aneurysms.

Looking at that information, we said, well, let's set a higher bar, at 50%, and try to beat that higher bar. And we agreed with FDA that if we could beat 50%, it represented a significant step up in the effectiveness for this difficult-to-treat patient population.

DR. EVANS: Same thing --

DR. CHER: With respect to safety, it was the same kind of

analysis. What I didn't show you was -- if we can find the slide right before that? What we did from the safety information was the same thing. From the safety perspective, we also had the benefit of several reviews of treatment of large and giant aneurysms written by surgeons reviewing surgical technique to treat these aneurysms, and these reviews, many -- we submitted many tables of these reviews to FDA -- would routinely give statistics saying that, you know, stroke and death rate was 15, 20, 25%. That information combined with the information that we abstracted from these full-text articles was very convincing to both us and to clinicians at FDA with respect to the study design.

DR. HURST: Dr. Ku?

DR. KU: Dr. Ku. With respect to the patients who had ischemic stroke and amaurosis fugax, did all of your centers evaluate the effectiveness of the aspirin and Plavix pre-device placement, because resistance to those two drugs has been described and is very often clinically significant.

DR. CHER: Could I ask you to elaborate on evaluate the effectiveness of aspirin and Plavix?

DR. KU: There are certain laboratory tests to assess the degree of platelet inhibition prior to device placement.

DR. CHER: Right. We did not include that in the study protocol. As far as I'm aware, at the time that we were developing the study

protocol as well as even to this day, I don't think that's a well-accepted method that would be applicable across all study centers. So we left that to the discretion of the treating physicians. Some of the physicians used VerifyNow. Other physicians I think used more clinical assessment. Other physicians told me that they don't think that the data for that system is suitable yet for evaluating the effectiveness of aspirin and clopidogrel. Nonetheless, in the clinical trial, it appeared to work fairly well. And the clinical management itself appeared to be sufficient.

DR. HURST: Dr. Brem?

DR. BREM: Beautiful presentation. I want to focus on just a little bit the exclusion of subarachnoid hemorrhage within 60 days of placement of the device. Firstly, can you elaborate why you did that, and do you have data about its use in the face of subarachnoid hemorrhage? And the second part of the question is in the mortality data in the historic control, it doesn't specifically say that the mortality that occurred within 60 days of subarachnoid hemorrhage is excluded. Is it separated out in that --

DR. CHER: Yeah, so with respect to subarachnoid hemorrhage, placing Pipeline requires the use of dual antiplatelet therapy, and we wanted to make sure that the trial that we were doing was -- you know, after all, it's a trial of an investigational device. We wanted to make sure that use of this new device was in a setting that was as safe as possible. For that reason, we did not want to treat patients in the setting of acute

subarachnoid hemorrhage. It's my understanding that the use of aspirin and Plavix in someone with acute subarachnoid hemorrhage is not a good thing.

So just like we excluded patients with acute subarachnoid hemorrhage, we also excluded patients who had had major surgery in the last 60 days. So, really, the focus of what we're doing is the treatment of unruptured aneurysms. With respect to --

Did you want to make any comment on that?

DR. BECSKE: Yes. I just wanted to say -- Tibor Becske again -- I just wanted to say that, as you know, to my knowledge, there is no randomized trial to look into this question of antiplatelet therapy in the face of acute subarachnoid hemorrhage. However, anecdotal evidence seemed to support the idea that probably it's not a safe practice. And so for that reason, we would like to probably discourage that. In many centers, based on this anecdotal evidence, the approach to these ruptured complex aneurysms has been that they first -- or we first coil them as much as we can to so-call protect them from rerupture and then, in a delayed fashion, put them on aspirin and Plavix and then stent support the previous coiling and finish the treatment. This is anecdotal information.

DR. BREM: Are you aware of anybody using, you know, the Pipeline device within the first 60 days of --

DR. BECSKE: Again, I have heard of maybe a handful of -- or less than a handful of cases. I was not present and I do not know -- these, I

believe, all occurred outside the United States. I was not present. None of my proctored cases involved any occurrence like that, so I cannot comment to that. Maybe Dr. Cher knows something.

DR. CHER: Yeah, I can. You know, as part of training and product release in Europe -- we're in close contact with the European practitioners, and I don't have the numbers at the tip of my fingers, but if you like, I can get them -- there have been a very small number of cases in which Pipeline was used in the setting of acute subarachnoid hemorrhage. And not surprisingly, I think we've had some poor outcomes, essentially, just from continued subarachnoid bleeding. And so we are not focused on that at all. And we would actually like to, as Dr. Becske said, continue to let physicians know that this is really a treatment for stable, unruptured aneurysms.

DR. BREM: And so just the final point on this, the mortality data on the slides that compares historically the very low mortality with the device compared to the natural history, does that exclude 60-day subarachnoid hemorrhage or does that include everything related to giant aneurysms?

DR. CHER: We did our best to try to extract mortality statistics from each article looking at only those patients who were treated in the setting of unruptured aneurysms.

DR. BREM: Thank you.

DR. HURST: Dr. Yang -- Kang -- sorry.

DR. KANG: Regarding your training and marketing plan, how much prior experience with other similar devices are you expecting for physicians who use these devices?

DR. CHER: The physician population that would use Pipeline are -- is interventional neuroradiologists as well as neurosurgeons with training in endovascular procedures. These are physicians who have typically been treating aneurysms via the endovascular route with coils for years. These are also physicians who have training in the placement of other intracranial devices, other intracranial stents, HDE-available stents. So these are physicians with a high degree of experience and a high degree of training in the use of devices that are not dissimilar from Pipeline. Those are really the intended physician population. So we start out with a physician population that has a high degree of expertise.

DR. KANG: And one follow-up question, then. Oh, I forget what it is now. Oh, did you get any feedback from the investigators on how difficult or easy the device was to use compared to other devices they've had experience with?

DR. CHER: The feedback from investigators was not only that Pipeline worked well and was deliverable but that there's no other way that they could have treated these aneurysms. And, you know, our investigators are, I can assure you, they're very happy, and the patients are very happy as

well.

DR. HURST: Dr. Richardson?

DR. RICHARDSON: I just want to ask a simple question. What concerns do you have regarding small vessels that are arising from the carotid artery in the area of the stent placement? For instance, you had several cases of amaurosis fugax. Did any of those proceed to blindness? And what about the anterior choroidal artery, things like that?

DR. CHER: So with respect to patients with amaurosis fugax, none progressed to permanent blindness or any permanent visual loss. With respect to covering the arteries, we did not assess ophthalmic artery flow specifically in the study. However, we did do a -- we did go back and look at the angiograms and look at ophthalmic artery flow in those patients in whom the Pipeline devices were covering the ophthalmic artery. I'm hesitating a little because this is information that we've not yet shared with FDA.

And we'll try to find that analysis for you, but in that analysis, the majority -- I believe it was around 800 -- slide up, please. So the ophthalmic artery was covered in 76 cases, and there was flow observed in the ophthalmic artery at 180 days in 63, or 83%, of those cases. In the cases in which flow in the ophthalmic artery was not observed, it's highly likely that the patient had flow to the retina through collaterals by the external carotid.

There may have been several instances of coverage of the anterior choroidal artery. However, we had no strokes that were related to coverage of the anterior choroidal artery.

And just to give some background here, when we initially discussed the study with FDA, part of the reason for choosing the internal carotid artery was because at that time, we did not have a lot of information about flow into side branches when covered by Pipeline. So we chose the internal carotid artery because it's a location in the brain where aneurysms occur, but there are not a lot of side branches to be particularly concerned about.

Does that answer the question?

DR. HURST: Dr. Posner?

DR. POSNER: Yes. There was a range and duration of the procedures, and I wondered whether the major modulators were accessed to the aneurysm or number of devices or something else that you might be able to control or expect to happen?

DR. CHER: Yeah. Placing Pipeline requires obtaining access to the distal parent artery with a guidewire and a microcatheter, and that was very often the longest part of the procedure. If you can imagine, the artery comes in here, the aneurysm is like this, and you have to find the hole, you know, the distal end at the other end of that artery. These guidewires, as you know, they're not -- you can't -- they're difficult to steer, and kudos to

the investigators in the trial. They did an excellent job at catheterizing the distal parent artery even in situations where it looked very, very difficult.

Once the distal parent artery was catheterized, the Pipeline placement actually went very smoothly and was, you know, was short compared to some of the maneuvers that were required. So in those cases where the procedure time was long, it was always catheterizing the distal parent vessel.

Tibor, did you want to say anything about that?

DR. BECSKE: Tibor Becske again. I fully agree with this statement. However, I would like to make a comment about the ophthalmic artery issue. So I would like to point out that it was a very detailed neuroophthalmologic examination, including retinal photography at baseline and at six months. So that is very important to know, I think.

DR. POSNER: Then one other question. On the cases where you did have to use multiple devices, the time between the decision and when it happens, and how do you decide it's time or why do you decide it's time to add extra devices and when is enough?

DR. CHER: Yeah. The devices available when we were doing the PUFS study were available up to 20 millimeters in length. Some of the aneurysms were -- the devices require anchoring in the distal parent vessel and anchoring in the proximal parent vessel. And a 20-millimeter device would not cover many of the aneurysms. So the primary reason for placing

multiple devices, one telescoped inside the other, is simply to span the entire neck --

DR. POSNER: (Off microphone.)

DR. CHER: Right. So what we tell physicians is, you know, you have to land -- the distal landing zone has to be a normal parent artery and the proximal landing zone also has to be a normal parent artery. And so we use the devices one at a time to build up a construct. So that's really the primary reason why multiple devices are used.

DR. HURST: Dr. Byrne?

DR. BYRNE: How long do you think these patients need to be followed up for the concern of stenosis, like late stenosis?

DR. CHER: The PUFS study goes to five years. There are angiograms that are planned at three and five years. Two-year follow-up began in November; three-year follow-up will begin November 2011. So the PUFS study already has built into it long-term follow-up. It's our feeling that the occurrence of stenosis inside Pipeline may follow time courses that are similar to other devices in other areas of the body, where the process itself may peak fairly early, for example, six months. So what we've observed is really no progression of stenosis from six months to one year. In fact, we have one case where there was major stenosis, asymptomatic, at six months, which at one year actually looked quite a bit better -- no intervention, just time -- looked better. So we suspect that, you know, it's highly unlikely to

have anything occur after the first year, but I don't have a lot of data to support that.

DR. BYRNE: Can these be followed up non-invasively? Is it reasonable to follow this with CTA or MRA?

DR. CHER: It may be. That's something that we've thought about. MR, the Pipeline interferes with MR, and it creates an artifact inside Pipeline. So it's very difficult to judge whether or not there is stenosis. Typically, what you see is what's coming in, there's a signal void where Pipeline is, and a lot of blood is coming out the other side, patient's asymptomatic. You can conclude what you would like to conclude from that. But, you know, so far, we have not approached FDA yet with whether other techniques can be done, and we're looking into that.

DR. HURST: Any other Panel questions for the Sponsors?

(No response)

DR. HURST: Fine. I'd like to thank the Sponsor's representatives for their presentation, and we'll now take a 15-minute break.

Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any member of the audience. We'll resume at 10:15.

(Off the record at 10:00 a.m.)

(On the record at 10:15 a.m.)

DR. HURST: The FDA will now give their presentation on this issue, and you have 75 minutes.

DR. HUTTER: Good morning, distinguished Panel members, members of Chestnut Medical, and audience members. My name is Joe Hutter. I am the team leader for the Pipeline Embolization Device for wide-necked intracranial aneurysms.

Chestnut Medical has submitted a premarket application to FDA for the Pipeline Embolization Device, or PED. PED was designed as a flow diverter device, which can be used in the treatment of intracranial aneurysms. There are no implants approved in the United States for the treatment of intracranial aneurysms with the mechanism of flow diversion.

This device is intended to be used in clinical situations in which standard coiling technologies have limited effectiveness. The PED was studied under IDE to evaluate the safety and effectiveness of the device system.

The following FDA staff members were involved in the review of the PED. The review team consisted of several clinicians with neurological and epidemiological expertise, a statistician, biologist for animal and biocompatibility tests, and biomedical engineers who are familiar with mechanical testing of implanted metallic devices.

Following this introduction and brief overview of the device itself, Dr. Rodichok will present a clinical summary, and Dr. Tarver-Carr will

discuss post-approval plan considerations.

The Pipeline Embolization Device is an implanted mass cylinder. It's cut from various lengths from the woven platinum and cobalt chromium alloy wires shown in figure 1. The device is deployed through a catheter, as shown in figure 2. An implanted device conforms to the walls of the parent artery and isolates the aneurysm itself from the primary blood flow, as shown in figure 3, taken from the Chestnut Medical patent.

As part of this IDE and PMA, FDA found that the PED passed rigorous mechanical and simulated functionality tests. Also, animal and biocompatibility testing was found to be adequate by FDA.

And now Dr. Rodichok will discuss the clinical data.

DR. RODICHOK: Good morning, distinguished Panel members and guests. I am Larry Rodichok. I'm a neurologist with the Neurodiagnostic and Neurotherapeutics Branch of CDRH. And as you just heard, I am the lead medical reviewer for this PMA.

My presentation will focus primarily on selected aspects of the data submitted that FDA believes merits a discussion by the Panel.

As a brief overview, although somewhat already covered by the Sponsor, intracranial aneurysms, or by the acronym IAs, are abnormal sacs usually found at one of the branching points of the major arteries at the base of the brain. As seen on the drawing on the left, such aneurysms are typically studied clinically by injecting radio-opaque contrast agents into the

artery by advancing a small plastic tube from the leg or arm. This procedure is called digital subtraction angiography. An example of angiography of a large such aneurysm is seen on the right.

Unruptured IAs may be found in as many as 5% of the U.S. population, which would represent 10 to 15 million people in the United States. Treatment of very small IAs is a matter of patient preference and physician judgment since the risk of rupture may be very long. However, as pointed out earlier, the risk of rupture increases with size of the IA. These account for approximately 10% of unruptured intracranial aneurysms. These large, which are defined as 10 to 25 millimeters in size, or giant, defined as over 25 millimeters in size, IAs most often occur along the carotid artery prior to the take-off of the posterior communicating artery and at the bifurcation of the basilar artery. As pointed out, the mortality when an IA ruptures is at least 50%, and those who survive often are left with serious disability.

The options for treatment of intracranial aneurysms are either surgery, primarily by means of what is called clipping, meaning placing a metal clip across the neck of the IA, which effectively eliminates it from the circulation, or endovascular treatment, that is, treatment by advancing a catheter into the parent artery and placing material into the dome of the IA to cause it to thrombose so that blood can no longer enter it. This material is most likely in the form of what is known as coils with or without the

assistance of a stent to block the mouth of the IA. A liquid embolic material that quickly forms a solid mass can also be used for the same purpose.

However, surgery is often not possible with the very large IAs, especially if there is a very large or unidentifiable neck. Endovascular techniques can also be limited in effectiveness for the large and giant IAs because of the large neck and/or dome in that they may be difficult to retain the embolic material within the IA and complete occlusion of the IA is difficult to achieve and recurrences do seem to increase over time. Therefore, there remains a significant unmet medical need for effective treatment of these large or giant wide-necked aneurysms.

As you have seen, the primary data submitted in support of reasonable assurance of safety and effectiveness of the PED device comes from the Pipeline for uncoilable or failed aneurysms, or the PUFS study. The data in the PMA was collected in the United States under an approved investigational device exemption as well as at sites in Hungary and Turkey. The study is a prospective, multicenter, single-arm, open-label study of the PED, which is ongoing since, as you have heard, follow-up extends to five years after treatment.

I would like to draw the Panel's attention to the key inclusion criteria that were instrumental in determining the eventual population studied. Eligible subjects must have had a single target intracranial aneurysm that was located in the petrous, paraophthalmic (which was to

include paraclinoid, ophthalmic and hypophyseal) segments of the internal carotid artery; and had a neck greater than or equal to 4 millimeters, or no discernible neck, and a size meeting maximum fundus diameter greater than or equal to 10 millimeters; and, finally, had a parent vessel diameter of 2.5 to 5 millimeters distal and proximal to the target IA.

These anatomic locations of IAs, as described here, including the terminology used for those locations, will be pertinent to the discussion of the proposed indications statement.

Similarly, the exclusion criteria that were key to determining the population studied were that subjects with more than one IA requiring treatment within six months were to be excluded. Subjects with a recent subarachnoid hemorrhage, defined as being within the last 60 days, were to be excluded, and with one exception, they were excluded. Subjects with a stenosis of the extracranial carotid or the IA's parent artery were also to be excluded.

Because we will be presenting some additional analyses of the data, I wanted to remind the Panel of the primary endpoints and success criteria for the trial. The primary effectiveness endpoint was a composite of complete IA occlusion at 180 days after treatment with no more than 50% stenosis of the IA parent artery and no use of other IA treatments, such as coils.

As you have heard, a Bayesian approach to the statistical

analysis was employed. Statistical success on the primary effectiveness endpoint was defined as a posterior probability of at least 0.975 that the endpoint was reached in more than 50% of the subjects at 180 days.

The primary safety endpoint was the proportion of subjects with death due to neurologic causes or major ipsilateral stroke at 180 days. For the purposes of this study and for this endpoint specifically, a major stroke was defined as one with a 4 point or greater increase in the NIH Stroke Scale score with a deficit that persisted for more than seven days and which occurred within 30 days of treatment. Whether a subject met the primary safety endpoint was adjudicated by an independent clinical events committee.

Statistical success on the primary safety endpoint, as you have heard, was defined as a posterior probability of at least 0.975 that less than 20% of the subjects met the endpoint at 180 days.

I will be presenting data regarding two of the secondary endpoints, namely, the complete IA occlusion rate at 180 days and at one year, as well as the incidence of stroke. These were components of the primary effectiveness and safety endpoints. There were no pre-specified success criteria for any of the secondary endpoints.

One aspect of the PED placement procedure that is an issue for Panel discussion involves the use of angioplasty balloons. While other IA treatments, such as coils or other stents, were not permitted in the trial, the

use of angioplasty balloons was permitted.

I would like to review some aspects of the study population since FDA has identified several analysis populations in addition to that reported by the Sponsor. In discussing the populations analyzed, we will distinguish between the term subjects and the term aneurysms, since two subjects in the study had a second qualifying aneurysm that was treated with the investigational device and included in the Sponsor's main analysis population. I will continue to use the acronym IA for intracranial aneurysms.

So of the 111 subjects enrolled, three were excluded prior to any attempt to treat and were not included in any analysis population. An attempt to treat was made in 108 subjects with 110 qualifying aneurysms. FDA has utilized this population in some analyses for which we have used the term IAs attempted population.

One of these 108 subjects was excluded from both the effectiveness and safety analyses since the subject was not treated with the device, leaving 107 subjects treated with PED as the safety population in both the Sponsor's and FDA's analyses of safety.

Three of these 107 subjects were treated with the device for what were deemed to be qualifying aneurysms by the investigator. These three subjects were subsequently determined by the core radiology laboratory to have aneurysms that did not qualify by size or location. These subjects continued to be followed by the Sponsor per the protocol, and we

do have follow-up data on those three.

Thus, there are 104 subjects in the Sponsor's effectiveness population. Since the protocol excludes subjects with two aneurysms requiring treatment and the statistical analysis plan describes the effectiveness population in terms of subjects, these 104 subjects' first-treated aneurysm may be considered an appropriate population for the analysis of effectiveness. This cohort of 104 subjects is referred to as subjects treated population.

However, finally, two of these 104 subjects did have a second qualifying aneurysm, which was treated with the device, and these were included in the Sponsor's effectiveness population, which is thus composed of 104 subjects with 106 aneurysms. We refer to this population as the IAs treated population.

Two subject characteristics that will be pertinent to subsequent discussions are as follows. The age range treated in the trial was from 30.2 years to 75.1 years. And the anatomic terms and locations used for those aneurysms treated were as follows. The two predominant locations were cavernous in 41.7% and paraophthalmic in 32.4%. The remaining locations, as described by the investigator, were petrous, carotid cave, superior hypophyseal, lateral clinoidal, supraclinoid, and posterior communicating, all of which occurred with an incidence of less than 10%. And you'll notice that the terms used by the investigators doesn't necessarily

correspond to the terms in the inclusion/exclusion criteria.

This table displays the lengths of the PEDs used in the trial. The vast majority of PEDs placed were the longer available lengths. Lengths greater than 20 millimeters were not studied.

The Panel will be asked to discuss the need for clinical data in support of the safety and effectiveness of PEDs greater than 20 millimeters in lengths not studied in the PUFS trial.

Almost all subjects required two or more PEDs. Nine required five or more, and one subject required 15 PEDs. The mean and median PED use was approximately three per subject.

And as you have seen, the mean total procedure time was approximately 120 minutes, with a maximum of 427 minutes. Perhaps more importantly, the mean total fluoroscopy time was approximately 50 minutes, with a maximum of 205 minutes. The median fluoroscopy time was 40.4 minutes.

There is one subject in PUFS with a fluoro time of 64 minutes, which is certainly not the longest, and a subject with an unknown fluoro time from the PITA study with adverse events of radiation-induced alopecia, an incidence of 1.4% for those two studies. Both were attributed by the investigator when we asked this question to prolonged procedures.

The Panel will be asked, therefore, to discuss whether the observed fluoroscopy exposure times during implantation of PED and the

adverse events just described support reasonable assurance of safety for the PED.

As noted earlier, the use of angioplasty balloons was permitted. In fact, in the PMA and the Executive Summary, it has been reported that 23 subjects required the use of angioplasty balloons. In a more recent communication from the Sponsor, that has been corrected to 22 angioplasty balloons and 18 subjects in the PUFS trial. Please also note that with only one exception, which is the one that coils were used, the PED alone was used to treat the target IA in PUFS.

We have also noted in a publication by Dr. Pedro Lylyk in his report of 180 subjects treated with PED that he notes that we don't have data on the use of this device with any other IA treatment. The current proposed labeling has no warning or precaution regarding the concomitant use of other devices.

Therefore, the Panel will be asked to discuss whether specific labeling, warnings, or precautions are warranted for the PED, given that in the PMA study, only limited use of ancillary devices, namely 22 balloon catheters and one use of coiling, was observed.

Also related to the procedure, investigators reported excessive friction in 5 of 52 subjects in PUFS in whom the Renegade Hi-Flo catheter was used to deliver the PED. Chestnut developed the Marksman catheter to reduce friction during PED delivery. There were no reports of excessive

friction in the 55 subjects during delivery with this catheter.

The Panel will then be asked to discuss the proposed labeling regarding microcatheter use in light of the issue of friction encountered in those 5 of 52 performed using the Renegade Hi-Flo catheter compared to no such issue in 55 subjects when the Marksman catheter was used. And the question essentially is should delivery of the PED be limited to the Chestnut Marksman alone or the two catheters used in this IDE study or any catheter with an 0.027-inch inner diameter.

I would like to point out some aspects of the analysis of the primary safety endpoint. As you have heard, as adjudicated by the clinical events committee, the primary safety endpoint occurred in six subjects, a rate of 5.6%, with an upper 95% limit of the credible interval of 11.7%. This result did meet the pre-specified safety success criteria that the probability of a rate less than 20% must exceed 0.975, which it did.

Two additional strokes, based on our review, should be considered major strokes, based on the clinical history provided. In addition, there were three subjects for whom medical outcomes were unknown or unclear, and thus, endpoint data is missing. The worse case for safety failures is therefore 11 out of 107, or 10.3%, with an upper exact 95% confidence interval of 17.7%, which does remain below the pre-specified success criterion of an incidence less than 20%.

Analysis of safety failures by subgroup, including a number of

additional subgroups that we asked the Sponsor to conduct, revealed no apparent differences in any subgroup, with the exception of those with hypertension. Subjects with hypertension met the primary safety endpoint. That is, they had a major stroke or neurologic death more frequently compared to those without a history of hypertension, and the unadjusted p-value for that difference is 0.087.

In fact, all six primary safety failures were in the group with hypertension, compared to no failures in the non-hypertension group. I should note that the overall incidence of hypertension in this particular study is 55.6%. Therefore, should this device be approved, we recommend an appropriate warning regarding safety in those with a history of hypertension.

The following slides highlight some selected categories of serious adverse events. The reported death rate of 2.8% or 3 out of the 107 assumes that the three subjects who withdrew or were lost to follow-up were alive. This can be assumed for one subject for whom there was no data at the 180-day endpoint but who did return and was alive and well without a major stroke at one-year follow-up. Thus, we believe the worst case death rate is 5 out of 107, or 4.7%.

This table summarizes adverse events of stroke in PUFS, and that includes both serious and non-serious adverse events. There are five peri-procedural cerebrovascular events and five post-procedural

cerebrovascular events with persistent neurologic deficits, for an incidence of 4.7% for each of those categories and an overall rate of stroke in the study of 9.3%. In addition, there were five adverse events of amaurosis fugax that occurred in four subjects, all of which, interestingly, occurred well past in the post-procedure period.

I would next like to point out selected analyses of effectiveness in PUFS. So as you have heard, 78 out of 106 aneurysms did meet the primary effectiveness endpoint of complete IA occlusion without significant parent artery stenosis. The two main reasons that 22 subjects did not meet the primary effectiveness endpoint were as follows. Fourteen of the 28 were due to persistent filling of the neck and/or dome of the aneurysm, and five were due to stenosis or occlusion of the parent artery.

This table shows the analyses of primary success criteria at 180 days for the three analysis populations I described earlier. So in the IAs treated population, 78 of 106 or 73.6% met the primary effectiveness endpoint. The posterior probability that the rate exceeded 50% was greater than 0.975. And, thus, the primary effectiveness success criterion was met.

Analysis of the primary effectiveness endpoint based on the 104 subjects treated in which we considered only the first aneurysm in the two subjects with a second qualifying aneurysm yields a success rate of 76 out of 104, or 73.1%, with a credible interval of 63.8 to 80.7%, which also would have met the success criteria for effectiveness.

Finally, for the primary effectiveness endpoint in the IAs attempted population of 108 subjects with 110 aneurysms, the success rate was 80 out of 110, or 72.7%, with an exact confidence interval of 63.4 to 80.8%, which still meets the success criterion of a lower limit rate of greater than 50%.

Thus, the primary effectiveness success criterion was met in all three of these populations.

All PUFS patients have been evaluated and are accounted for at the one-year assessment. This table shows the primary effectiveness endpoint results at one year. At one year, there were 75 subjects in the IAs treated population of 106 aneurysms who met the primary effectiveness endpoint. This represents a success rate of 70.8% with an exact 95% confidence interval lower limit of 61.1%.

For the subjects treated population of 104 subjects, the success rate was 70.2% with a lower limit of the exact 95% confidence interval of 60.4%. And, finally, for the all attempted population of 110 aneurysms, the percent effectiveness success was 77 out of 110, or a rate of 70% with a lower limit of 58.6%. The result in each of these populations is statistically significant and appears to be stable compared to the result at 180 days.

We would like to highlight the analyses of some additional selected endpoints. An important secondary endpoint is the incidence of

parent artery stenosis or occlusion since this is a concern when a device is implanted within an artery and such a stenosis or occlusion could result in stroke now or in the future. Relevant to this analysis, it should be noted that of the 104 subjects, 97 subjects with 99 IAs completed the 180-day angiogram, and 89 subjects with 99 aneurysms completed the one-year angiogram. All three additional subjects that we have added to the attempted population did have angiogram at 180 days and one year, and thus, we do have data for that population.

We have calculated the incidence of parent artery stenosis, including total occlusion, for the IAs treated and the IAs attempted analysis population, imputing the worst result for those subjects for whom data was absent. With that analysis, at 180 days, the incidence of stenosis of 50% or more, including total occlusion, was 10.4% in the IAs treated and 10.0% in the IAs attempted population. At one year, the incidence was 11.3% in the IAs treated and 10.9% in the IAs attempted population.

Since the risk of a recurrence of the aneurysm, as you have heard, increases when complete IA occlusion is not achieved and it is also important that an initial complete occlusion be sustained over time, we have calculated the rate of complete IA occlusion using the same imputation method I just described for the parent artery stenosis or occlusion rate.

So with that analysis, at 180 days, the rate of total IA occlusion was 76.4% in the IAs treated and 75.5% in the IAs attempted population. At

one year, the rate was 73.6% in the IAs treated and 72.7% in the IAs attempted. Based on these data, the total occlusion rate appears to be stable from six months to one year.

The Sponsor has proposed this following indication for use in its submission. The Panel will be asked to discuss the question as to whether modifications to this proposed indication for use statement are warranted, specifically regarding the youngest appropriate age, specification regarding rupture status of the target aneurysm, appropriate terminology for the anatomic location of the target aneurysm eligible, along with any other modifications that the Panel might recommend.

Now, Dr. Michelle Tarver-Carr will discuss the post-approval study considerations.

DR. TARVER-CARR: Good morning, Panel members and guests. I am Michelle Tarver-Carr. I am an ophthalmologist and epidemiologist in the Division of Epidemiology within the Office of Surveillance and Biometrics in CDRH. I will be discussing the applicant's proposed post-approval study.

Before we talk about post-approval studies, we need to clarify a few things. The discussion of a post-approval study, called a PAS, prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting that the device is safe and effective. The plan to conduct a post-approval study does not decrease the threshold of evidence required by FDA for device approvable. The premarket data submitted to

the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate risk/benefit analysis.

There are two general principles for post-approval studies. The main objective is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable evidence of device safety and effectiveness. Post-approval studies should not be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.

The reasons for conducting post-approval studies are to gather postmarket information, including longer-term performance of the device; data on how the device performs in the real world, in a broader patient population that is treated by community-based specialists as opposed to highly selected patients treated by investigators in the clinical trials; evaluation of the effectiveness of training programs for use of devices; evaluation of device performance in subgroups of patients since clinical trials tend to have a limited numbers of patients or no patients at all in certain vulnerable subgroups of the general patient population; monitor adverse events, especially rare adverse events, that were not observed in the clinical trial. In addition, post-approval studies can also address any other issues that may be identified by Panel members based on their expertise.

Post-approval studies should contain a fundamental study question or hypothesis, safety endpoints and methods of assessment, acute and chronic effectiveness endpoints and methods of assessment, and the post-approval study should specify the duration of follow-up.

Since we have covered the important considerations for a post-approval study in general, I will now describe the proposed study for the Pipeline Embolic Device. Please note that in addition to the IDE premarket study called PUFS, the Sponsor is conducting a continued access study called PUFS-CA which is still enrolling new patients. PUFS and PUFS-CA have identical inclusion and exclusion criteria and nearly identical protocols. These patients were consented upon enrollment for five years of follow-up. These two studies form the basis of the post-approval study cohort.

The FDA review team has identified the following postmarket questions as relevant for the PED. Is the device safe in the longer term for the proposed indicated patient population? Does the device continue to be effective with longer follow-up? Given the variable natural history of those who experience aneurysms at or below the cavernous segment, compared to those who experience them at or above the ophthalmic segment, would the device perform similarly with respect to effectiveness and safety in the longer term in both anatomic locations?

The study design proposed is a prospective, single-arm,

multicenter cohort study to assess the longer term safety and sustainability of the observed treatment effect. The sample size at baseline is anticipated to be 105 subjects with analyses also being conducted for two subgroups based on the anatomic location of the aneurysm. Participants will be followed for five years after treatment by telephone interviews in years two and four and by clinical visits with angiograms in years three and five.

The study hypothesis on which the sample size is based is to determine whether the incidence of ipsilateral stroke and neurovascular death with the PED device will be less than 25%.

Secondary analyses will be performed to examine the rate of complete occlusion over follow-up and the device-related adverse events. The analysis of these outcomes will involve survival techniques and descriptive statistics.

The primary safety endpoint is ipsilateral stroke or neurovascular death at five years. Ipsilateral stroke is defined by the Sponsor as a focal neurological deficit of presumed vascular origin that persists more than 24 hours with a neural imaging study that does not show a different etiology. This definition includes signs of subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction, retinal artery occlusion or retinal emboli. If a participant dies or undergoes cerebrovascular surgery prior to meeting the 24-hour criteria, they will be classified as experiencing the primary safety endpoint. Neurovascular death

is defined as any cause of death related to the neurovasculature, for example, arterial dissection or mycotic aneurysm.

The secondary objectives of the study are to describe the rate of complete occlusion of the aneurysm over follow-up. This will be evaluated at a core laboratory using the same criteria as described for the original PUFS study. The applicant will also report whether additional procedures, including stent use or coiling, were subsequently employed to achieve complete aneurysmal occlusion at five years.

The last objective is to describe the rate of device-related adverse events. The adverse event list is identical to the ones used in the premarket study.

As of the most recent report from the applicant, there were ten patients in the PUFS study who experienced a stroke within the first year after surgery and three subjects who withdrew, leaving 94 subjects at risk for a late ipsilateral stroke or neurovascular death. The continued access study has currently enrolled 11 participants. The study is still enrolling one to two subjects per month at two clinical centers. Hence, it is possible for there to be more than 11 subjects from this cohort at the start of the post-approval study.

The applicant anticipates a 15% lost to follow-up by three years and a lost to follow-up rate of 10% between years three and five, thus leaving a sample size of 78 participants. Assuming that half of the sample

has aneurysms at or above the ophthalmic segment or at or below the cavernous segment, the subgroup analyses should be of adequate size to make statistically powered inferences.

In light of the proposed post-approval study, the Panel will be asked to comment on the primary outcome proposed by the applicant of any ipsilateral stroke or neurovascular death and whether it adequately captures the safety concerns associated with this device. If the Panel thinks that this primary outcome is not sufficient, please suggest other outcomes that should be considered.

Please comment on whether the proposed safety threshold of less than 25% for the primary endpoint is reasonable for this device with its intended use population.

Please comment on whether there are other subgroups in addition to the two proposed anatomical subgroups that are important to analyze.

Please comment on whether the proposed post-approval study addresses all the potential concerns with the use of the Pipeline device or whether additional post-approval studies are warranted.

Thank you for your attention. This concludes the FDA presentation. We'd be happy to entertain any questions at this time.

DR. HURST: I'd like to thank the FDA speakers for their presentations.

Does anyone on the Panel have a brief clarifying question for the FDA? Please remember that the Panel may also ask questions to the FDA during the Panel deliberations session later this afternoon, and please remember to state your name prior to speaking.

Dr. Ku?

DR. KU: Andrew Ku. Point of clarification, the FDA provided the Panel members with an Executive Summary. Are we permitted to ask questions from that or only from the presentation?

DR. EYDELMAN: From anything that we provided.

DR. KU: Anything provided? Okay. There was a section in the Executive Summary, which I'm sure the Sponsor submitted, on the baseline characteristics, Table 8 of the PUFS patients with a *n* of 108 patients. And they noted a cranial neuropathy of different cranial nerves. And by my count, the *n* of patients with cranial neuropathies, or the number of cranial neuropathies, was 71. And then in Table 9, there was a prevalence of baseline intracranial neuropathy by aneurysm size and -- by size. And somehow, that one has an *n* of 108.

So I didn't understand why in one table which covered all the patients and in another table which covered all the patients there were differing numbers of baseline cranial neuropathy.

DR. EYDELMAN: If I can just ask for clarification, are you referring to the FDA Executive Summary or the Sponsor Executive Summary?

DR. KU: FDA Executive Summary.

DR. EYDELMAN: Okay. Thank you.

Do we have that information or do we need to get back?

DR. RODICHOK: I have the tables, but I don't have an exact answer to your question. I will have to look into that one.

DR. KU: And let's see, another question that perhaps maybe the Sponsor could identify, this was in a different table -- it was in Table 16, which was deviations regarding eligibility criteria in PUFS. And on the third page of that, which is actually page 48 of 72, or governing that overall section, there was apparently one intracranial hemorrhage, and the patient was on both Coumadin as well as dual antiplatelets at the time. I believe that was actually post-operative. And a question that I have is does the Sponsor have any feeling as to whether dual antiplatelet therapy with Coumadin is something that should be a warning or if they would consider, you know, single antiplatelet versus no antiplatelet in those situations?

DR. EYDELMAN: I just wanted to clarify this time is allotted for questioning the FDA staff.

DR. KU: Okay.

DR. EYDELMAN: If you have questions specifically to the Sponsor, please reserve it to the later time.

DR. KU: Right.

DR. RODICHOK: I could point out that that patient is the one

with Factor V Leiden coagulopathy. The Coumadin was reinstituted, understandably, as soon as possible. So there was much debate over that subject, I think, in everybody's minds, and that's a rather exceptional situation.

DR. KU: Um-hum.

DR. HURST: Other Panel members, questions for the FDA?

Yes, Dr. Yang?

DR. YANG: Sorry, Lynda Yang. I was wondering, given that it seems that complications may occur in places that are lower versus high volume, and there was mention of training on the labeling about the need for five proctored cases, does the FDA have a comment on whether they think that's enough? Is that the usual?

DR. HUTTER: I think we would welcome Panel input on that issue. There is a table in your Executive Summary that has a hint that, as one might guess, the safety improves as the number of cases at least gets over ten, but we would welcome your neuroradiologic expertise into just exactly how the training should be planned.

DR. HURST: You know, my comment on that is that's a lot of proctoring. That's quite a bit of proctoring, five cases, particularly for people who have been involved in interventional neuro. So I think that, if anything, you know, that's well over onto the safe side.

Yes?

DR. YANG: So I understand the part about experienced neurointerventionalists, but I don't think that's ever actually indicated anywhere. That's an implied statement. Is that correct?

UNIDENTIFIED SPEAKER: (Off microphone.)

DR. YANG: The point being that for an experienced neurointerventionalist, I would agree that five cases is probably reasonable, but I don't think that that's actually stated anywhere, or is it?

DR. EYDELMAN: To my knowledge, there's no restriction to experienced neurointerventionalist surgeon anywhere in this labeling, the word experience.

DR. HURST: I mean, I think my point was just that that's quite a high number of proctored cases for any newly approved device that I've seen in a very long time, so that if that's, you know -- and, of course, it is designed to enhance safety -- that's quite a number of cases to enhance safety.

DR. YANG: And my only point was whether or not that's something that needs to be included in, you know, the actual label.

DR. EYDELMAN: Once, again, we'll welcome your recommendations if the Panel has concurrence.

DR. HURST: Other questions, comments?

(No response.)

DR. HURST: Thank you.

We also had some earlier questions for the Sponsor, and I wonder if those answers are available at the present time.

DR. CHER: Daniel Cher, Chestnut Medical. There was a question about -- I'm sorry, may I answer the question? Yes? Okay.

DR. HURST: Yeah.

DR. CHER: There was a question about six patients -- this was from Dr. Yang -- six patients in which Pipeline could not be delivered or there was an issue in delivery of Pipeline. In five of those cases, the Pipeline device could not be passed all the way through the Renegade Hi-Flo catheter because of excessive resistance. In all of those cases, the Renegade catheter with the Pipeline device inside of it were simultaneously removed, consistent with what we recommend in the IFU. A new catheter was placed and the procedures were finished. So all the patients were successfully treated.

In another case, one of the Pipelines was delivered, but its location after delivery was not in the right place, but again, that procedure was successfully finished.

There were three serious adverse events amongst those six patients. The first patient had a caudate nucleus hemorrhage about five days after the procedure. He was hospitalized. He showed minor word finding difficulties and some confusion. He was treated with an EVD, and over the course of the next few days, it cleared and he was fine thereafter.

At six months, his aneurysm was completely occluded.

The next patient was a complex patient, and later I can pull up some more of the history, but this was a man with a history of ischemic -- I'm sorry -- non-ischemic cardiomyopathy who had a history of ventricular arrhythmias, history of multiple antiarrhythmic drugs, ejection fraction less than 30. He experienced a sudden cardiac death on post-operative day four. Again, we think that was unlikely to be due to the catheter.

The third patient is a patient who awoke from the procedure with questionable ischemia. She had some confusion. This was just the morning after the procedure. And the physicians were, despite a negative CT scan, the physicians were concerned about ischemia. They gave a dose of IV tirofiban, which is Aggrastat, and the patient subsequently had a intracranial hemorrhage. She had a major stroke, which counted towards the primary safety endpoint. By day 30, she was actually neurologically normal. She did very well. At 180 days, her aneurysm was completely occluded.

I think, in summary, we did not see any relationship between inability to deliver a Pipeline through a catheter and these adverse events.

Does that answer the question?

Okay.

DR. HURST: Mr. Mueller?

MR. MUELLER: Yes. Dave Mueller. On those five where there

was friction and you had to withdraw the catheter, you said a new catheter was put in and the Pipeline was delivered?

DR. CHER: Um-hum.

MR. MUELLER: Was that the same brand of catheter or which catheter was it?

DR. CHER: It was the same brand of catheter. So at the time that we were beginning the PUFS study, we were using -- we were asking physicians to use a commercially available catheter, Renegade Hi-Flo. Another catheter called Mass TRANSIT was also in the study protocol that could be used. These were the two catheters that we had tested and showed the ability to deliver Pipeline. We did know, though, in experience in the PITA study, that these catheters were not optimal. We therefore designed our own catheter, the Marksman catheter, and that became available roughly midway through the study. When Marksman became available, the physicians expressed a strong degree of preference for that catheter. I heard from multiple physicians "night and day."

So this is not to say that Pipeline delivery is impossible with the other catheters. It certainly can be done, and we completed the PITA study with those other catheters. However, the Marksman catheter has design aspects of it that are specifically related to the ability to deliver Pipeline, and it appears that physicians prefer that device.

MR. MUELLER: Was there return product analysis on the five

that had high friction, and if so, what was the cause of the high friction? Was it a design element or some other element?

DR. CHER: Yeah. It's a design element, and you'll have to forgive me, I'm not a design engineer, but the distal tip of the Renegade Hi-Flo is not reinforced with braiding. And what that means is that when there's friction, it can tend to stretch the distal portion of the catheter and that makes delivery more challenging. The changes that we made for Marksman were to increase the amount of braiding of the catheter so as to make the distal end of the catheter a little bit stronger so that it would resist ovalization in tortuous vessels.

Let me re-explain that because I don't think I did a very good job. I apologize. We're placing this catheter into very tortuous anatomy, in the carotid siphon. It's, you know, it's one of the more tortuous areas of the brain. When the Renegade Hi-Flo catheter turns tight corners, because it does not have as much reinforcement on the distal end, the inside of the catheter can ovalize, and that ovalization will increase the interaction between the Pipeline device contained within the catheter and the inside -- the inner diameter of the catheter.

So what we did with Marksman was to extend that area of reinforcing a little bit more distally to make the distal end of the catheter a little bit stronger so that as it goes around tight curves, it does not ovalize, and by resisting ovalization, there's less resistance.

That was hopefully a better explanation.

MR. MUELLER: Thank you.

DR. HURST: Yes, Dr. Duehring?

DR. DUEHRING: Dr. Duehring. I'm the Consumer Rep. In your experiences in the last five years, post-placement, are there any restrictions as far as, like, CTAs or MRAs? Does it cause artifacts? Are they MR-compatible at a higher tesla?

DR. CHER: Yeah, there are no restrictions. CT angiogram is commonly performed, and there's no interaction between x-rays and a metallic implant. It is radio-opaque on CT, so it can be very useful. There are definitely MRI artifacts, and we have described those in great detail to FDA. The artifact is within about 2 millimeters of Pipeline; there is a distortion of the signal. We have also done extensive benchtop testing of MRI interaction with short bore higher tesla MRI scanners and shown that there's no effect on temperature and nothing to be concerned about. So patients can get MRIs, and patients can get CT angiograms, you know, at the discretion of their physician.

DR. DUEHRING: Okay. Thank you.

DR. HURST: Other Panel questions for either the Sponsor or the FDA? We're early, so we have additional time in which to ask any questions.

Yes, Dr. Eydelman?

DR. EYDELMAN: After the Panel completes the questioning of the Sponsor, we have the answer to Dr. Ku's earlier question to the FDA.

DR. HURST: Okay. Dr. Byrne?

DR. BYRNE: We're being asked to consider changing the age, modifying the age, for the indications and, you know, specifically looking at the youngest appropriate age, in reality, most of these aneurysms occur in older patients, and there really is no top age for these things to occur. Should we be considering extending the age to older patients?

DR. CHER: From our perspective, we did not propose any age restriction, but we have treated patients up to -- I believe our oldest patient treated was 87 years old. Youngest patient treated, 13 years old. I agree with you that large and giant aneurysms are quite rare in children and, you know, we haven't brought a whole lot of information to support safety and effectiveness in that particular subgroup. At the same time, it would be unfortunate if that use were deemed off label, from the physician's perspective.

DR. HURST: Dr. Ku?

DR. KU: Andrew Ku. This is in the FDA Executive Summary, and I was reviewing the heparin dosage as well as the incidence of intracranial hemorrhages as well as ischemic strokes, and even though it's not statistically significant, I noticed that in the patients who had lesser doses of heparin administered per kilogram were the patients who had a

stroke, and in the patients who had the relatively higher dosage of heparin administered, that they had intracranial hemorrhage, which was not seen in the ones with the lower heparin doses. Is that basically clinical judgment or any particular recommendation from the manufacturer?

DR. CHER: Is this question for the Sponsor or for FDA?

DR. KU: More for the Sponsor --

DR. CHER: Yeah.

DR. KU: -- because the physicians usually determine how much heparin they give to the patient --

DR. CHER: Right.

DR. KU: -- during the procedure, and I assume your patients are fully heparinized during the procedure in addition to antiplatelet therapy.

DR. CHER: Right. So we had discussions with FDA about this aspect of the protocol when we designed the protocol. And it was a desire on the part of both FDA and the Sponsor to standardize to some degree heparin dosing. And so we asked the physicians to use heparin dosing within 50 to 100 milligrams per kilogram. And many of the physicians adhered to that. Many of the physicians provided doses that they thought were most appropriate. And I think at this point, you know, as you noted, the statistical association is not statistically significant, and I think what you're implying, and it's certainly what we would agree with, is that really this is a clinical

decision and should be left to the discretion of the physician.

DR. HURST: Yes, Dr. Kang?

DR. KU: Peter Kang. It seems like most of the patients who were treated in the study, in the PUFS study, had more than one PED device placed. Is there any risk of -- I assume that these devices are sort of overlapping at the ends. Is there any risk of them separating that you were aware of?

DR. CHER: There is a risk of separation. We did not observe it in PUFS. We've observed it extremely rarely in the commercial setting. And this really, I think, is a training issue. During training, we ask the -- you know, we instruct the physician how to best overlap the devices as to prevent separation, but it's really been extremely rare.

DR. HURST: Dr. Becker?

DR. BECKER: Hi. Kyra Becker. You know, looking at Table 17 again, with the heparin dosing, it looks like there's a fair number of non-intracranial hemorrhagic complications. My calculations look about 10% of patients have groin hematomas or problems related to bleeding there. And I was wondering if you think that's related to heparin or that's the aspirin, the clopidogrel or a combination of all of the above, and what precautions can be taken to avoid groin hematomas and continued bleeding and retroperitoneal hematomas?

DR. CHER: I'll give my answer. Then I'll ask Dr. Becske or

actually Dr. Lanzino to give a response as well. Aspirin, clopidogrel, and heparin are routine for endovascular procedures in which endovascular implants are placed. Any occurrence of, for example, groin hematomas or non-neurologic bleeding are related, you know, to the combination of these three agents. They obviously have nothing to do with Pipeline. It's an area that goes beyond my expertise, and I think I'd best let the clinicians decide that. But I do want to let you know that this is, you know, absolutely routine in these procedures.

Dr. Lanzino, did you want to comment on that?

DR. LANZINO: I think the incidence of groin complications is probably multifactorial. There are different ways that operators establish hemostasis at the end of the procedure, some by minor compression, others with different types of closure devices. Also, some of these patients were left on heparin, fully heparinized for a short period of time after the procedure. Others, the heparin was not reversed on purpose at the time of establishing -- trying to establish hemostasis. In those, it has a little bit to do with the strict definition of groin hematoma. It is not that unusual, especially in these patients with dual antiplatelet therapy and on heparinization that we do see a small amount of hematoma that is often not clinically significant.

DR. HURST: Thank you. You know since it has been brought up, how did you come to the number of five proctored cases? You

mentioned that in your presentation.

DR. CHER: Yeah. Understand that the physicians who are using this device are interventional neuroradiologists, neurosurgeons with training in endovascular. These are physicians who are very familiar with the placement of other intracranial devices, even intracranial stents. So these are physicians who already have a substantial amount of expertise in placing these devices.

The overall design of Pipeline is similar in many ways to the use of other intracranial implants, so there's not a lot of differences. The differences are minor and they're technical. We also received feedback from training of physicians in Europe and in other areas of the world. And that training is -- that training program is similar. And what we've been told is that a minimum of five is a reasonable number.

DR. HURST: Dr. Ku?

DR. KU: Your current longest stent is 20 millimeters, and in your design specifications, I guess it goes up to 35 millimeters. I'm assuming that the longer stents underwent the same amount of mechanical testing, as far as durability for lifespan?

DR. CHER: That's correct. Understand that the difference between a -- let me give you some background here. During the PUFS study, the implants were available up to 20 millimeters in length, and as you saw, device placement with those devices was successful in the vast majority of

cases. However, we received feedback from physicians that longer devices would be beneficial, might make the procedure a little quicker and might allow the procedure to be done better.

Based on that, we prepared devices that were 25, 30, and 35 millimeters in length, and there were some engineering things that we had to deal with, with respect to deliverability. But we tested all those and confirmed all those. But I just want to emphasize for you that the primary difference between a 35-millimeter device and a 20-millimeter device is that we cut the device 1.5 centimeters longer. So the device is exactly the same thing. It's just cut to a longer length.

So we did all the basic testing that's required for these devices, submitted that to FDA. FDA did approve adding those devices to our IDE study. Those devices are now on the market in Europe as well since September 2010. At this point, we have really a small amount of information, but I can confirm for you that -- a small amount of information about their use. Nonetheless, I can confirm for you that there was substantial testing of those devices.

DR. KU: Okay. And second question is with the longer stents, typically, the longer the stent, the greater the potential mechanical friction in delivering the device. With your bench testing of it, was there a significant increase in -- or decrease in deliverability versus increase in, you know, amount of force that you needed to push the stent to deploy it?

DR. CHER: Yeah. That indeed is the key issue. A longer device will have a longer surface area over which the device and the catheter in which it's contained can interact. We did make very minor design changes, which we've, you know, summarized in great detail for FDA, to optimize the delivery of these longer devices. We did animal study to confirm them. And, again, these devices are, you know, very recently on the market in Europe, and we're getting good feedback about those devices.

DR. HURST: Mr. Mueller?

MR. MUELLER: Yes. Dave Mueller. On these longer devices, are they, in your opinion, going to become the standard length, or are these more for the huge aneurysms that have a longer span that you really want, so the number of cases they're going to be used in is less comparatively to kind of a workhorse size?

DR. CHER: I agree. The purpose of having the very long device is to reduce the amount of telescoping that a physician would need to do in an extremely long aneurysm. Many of the aneurysms in PUFS, although they were large and some of them giant, could be treated with the devices we had up to 20 millimeters in length. But the longest devices that we're talking about are really only going to be used for those extremely long, very complex aneurysms. There's no reason to use a 35-millimeter device with a 12-millimeter aneurysm.

MR. MUELLER: Yeah. So to try to obtain clinical data on these

extremely long ones, you're already looking at a rare event, so to speak, when you have an extremely long aneurysm?

DR. CHER: Indeed.

MR. MUELLER: Thank you.

DR. HURST: Dr. Evans?

DR. EVANS: Scott Evans. I just wanted to clarify a little bit of terminology, and I think it's a minor issue, but I want to ensure myself that it is so.

The PUFS study is described as a single-arm study, but you use the term historical controls a few times, which usually means that there's a second group of patients that's being compared to. And I think you meant it in the fact that -- in the manner in which you used historical data to inform you about how to select an appropriate bar for effectiveness and an appropriate bar for safety.

And although I have some minor disagreements with who should be in the denominator when you're assessing effectiveness, when you do some sensitivity analyses, regardless of how you treated this few number of patients, your effectiveness result is strong enough to hold up regardless of what you do. And similar, in safety, there's some questions about whether a few more events should be counted in the numerator. And, again, regardless of how you treat them, sensitivity analysis seems to show that your bar has been met and you have strong data in that way.

The reason I bring this up, and in particular, in your effectiveness evaluation, it seems like the historical data seems to suggest that, you know, the occlusion rate and your endpoint rate in historical terms was far lower than the bar you set, and you set a pretty high bar for yourself and met it quite well. For safety, this is perhaps less of a buffer zone.

And the reason I bring up the distinction between the historical control acting as a true historical control versus whether you're just comparing to a rate observed in historical controls is because there's a distinction between saying that your safety event rate is less than 20% compared to saying your safety event rate is less than a historical control group that displayed a 20% rate. And the reason is that, in the latter case, there's uncertainty. Any time you observe on a rate in any particular trial, it's measured with error. It's just an estimate. And so there's variability associated with that. So there's a slight distinction between saying that you're comparing to a historical control and whether you're doing better or worse or similar to that group versus saying we've simply shown that the event rate is, say, less than 20%.

So I just wanted to clarify the terminology that was used in that we have this single-arm trial, but yet there was some discussion about, you know, "historical controls."

DR. CHER: Okay. Noted.

DR. HURST: Thank you, Dr. Evans. I believe the FDA is

prepared to answer Dr. Ku's earlier question.

DR. RODICHOK: Yes. Larry Rodichok from the FDA again. Before I do that, I would comment on the question about non-serious hemorrhagic events and what they might be due to. In our analysis, the vast, vast majority of those were well beyond the time when heparin was being used. So my guess is there were more along the lines of those related to antiplatelet agents.

Regarding the question of Tables 9 and 8, so the number 108 is the total number of aneurysms being included in the table, and that's the total number that had the clinical evaluation.

DR. HURST: Excuse me, could we just repeat the question. This was the question regarding the incidence of cranial neuropathy, right --

DR. RODICHOK: The question was there's a discrepancy -- right. The number of patients listed in Table 8 with cranial neuropathy, which add up to 71, and the *n* for that table is 108, and in Table 9, where the *n* is also 108, and actually, what it adds up to is 72. So there is a discrepancy of 1. And the *n*'s down the second column are the number of aneurysms in that category from which the percentages along that row are calculated. So there is a discrepancy of 1. It's a subject with cranial nerve 6 that somehow or other there's more -- there's one discrepancy there. But otherwise, that's the explanation.

DR. KU: Okay. Yeah. I just looked at the wrong part of the

table. Okay.

DR. HURST: Other questions for either the FDA or the Sponsor?

(No response.)

DR. HURST: Because we do have some additional time before lunch, we're going to begin the Panel deliberations by beginning to address the FDA questions. Let me just say that although this portion -- and we're going to come back to the portion again after lunch to allow the public speakers to speak.

Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. Additionally, we've requested all persons who are asked to speak identify themselves each time. It, again, helps the transcriptionist identify the speakers.

So we're going to focus at this time on the FDA questions. Copies of these questions are in the folders. And, again, I'd like to ask each Panel member to identify him or herself each time she speaks to facilitate transcription.

Dr. Joseph Hutter will present the FDA questions. Dr. Hutter, if you'll present the first question, please?

DR. HUTTER: The current PMA contains no data for PED lengths greater than 20 millimeters. Given the absence of clinical evidence

for PEDs greater than 20 millimeters in length, do you believe that additional clinical data are necessary to determine the safety and effectiveness of these longer lengths?

DR. HURST: Yes, Dr. Yang?

DR. YANG: Lynda Yang. Could I ask a question of the Panel members that have experience with this? Is it harder or more difficult to place telescoping kinds of devices or is it more difficult to place one very longer device that might be hard to maneuver across these?

DR. KU: It really depends on how much friction it takes to push the stent out. If you're able to push it out, it's much easier to deal with one than to deal with two. Any time you are dealing with more than one stent, when you're trying to attempt to put a second telescoping stent in, you run the risk of the device moving inadvertently on you and not deploying in the proper position.

So, in general, you know, if you have to do two telescoping stents, it's much easier to do two long ones than to do three or four short ones to get the same length. So the preference is to do the procedure once rather than twice.

DR. HURST: I would agree with that absolutely. In many cases, it becomes quite a bit more complex to put two devices in close proximity to one another.

DR. YANG: May I follow that with a question? So when you're

doing that and you mentioned that it's the friction, have you noticed in your experience a difference in friction between, like, a 15 millimeter and a 30 or is that --

DR. KU: Yeah. The difference can be significant. That's why I asked the manufacturer as to, you know, on their bench testing what their information showed. Usually, if it's a, you know, difference in force of maybe 10, 20%, you can get away with it. A lot of it does relate to the delivery device, which the manufacturer has commented on that. The delivery devices can be modified both now and in the future to permit easier delivery. A lot of it is materials compatibility and a lot of other factors.

DR. HURST: Other questions?

(No response.)

DR. HURST: Then Dr. Eydelman, I get the sense of the Panel that it's our sense that probably there is no need to do further determinations with respect to the longer stents.

DR. EYDELMAN: All right. Thank you.

DR. HURST: Question 2?

DR. HUTTER: Fluoroscopy exposure times during implantation procedures in the pivotal study range from 8 to 205.6 minutes. Two subjects experienced radiation-induced alopecia. Do the observed fluoroscopy exposure times and adverse events support a reasonable assurance of safety for the PED?

DR. HURST: Dr. Becker?

DR. BECKER: If I recall, it sounds like the one patient in PUFS who had alopecia had a fluoroscopy time of about 60 minutes, so it was not that long. And so I guess I'm wondering, in light of a lot of the recent publicity around the CT scanners and radiation doses not being monitored, is that a possibility with fluoroscopy as well, where the actual amount of radiation in different devices and different institutions could differ?

Does anybody know the answer to that?

DR. BREM: I think one issue is that there's a different sensitivity. Patients are sort of randomly patients who have more severe reactions to radiation for brain tumors, for example. So I just think that there's a certain amount of unpredictability about the reaction to the same amount of radiation.

DR. HURST: Yes, Dr. Posner?

DR. POSNER: Yeah. This is Dr. Posner. I can speak for our experience in our cath labs at University of Florida. And we basically had standardized levels that varied from pediatric to adult patients. Again, the pediatric patients were given much less exposure time. And we had the timers going during the procedures for cardiac caths, which is what we were doing. And the clinician knew where they were on the clock and they knew if they had to terminate early or whatever. So it was basically set up by experience in the clinician and the institution as to what the exposure time

was going to be.

DR. HURST: You know, I might also add to that that institutions are in fact responsible for monitoring their own radiation exposure. And the process that they go through in doing that is to look at high radiation exposures, then evaluate the equipment, then evaluate the technique. All of these have a very significant effect on radiation exposure in an individual type of case. I might also say that these exposure times, even as measured by something that's considered to be relatively crude, like fluoro time, does vary considerably from case to case. And that can depend on the tortuosity of the artery, how difficult it can get into the artery. I believe that the mean fluoro time was 48 minutes. And the Sponsor can correct me if that's incorrect. That I'm not sure is terribly different from some recent publications, in fact, that I've seen with respect to AVM embolization with Onyx, where per procedure fluoro time in an article in 2008 in *Neurosurgery* was 57 minutes plus or minus 26. So these are not trivial doses in any sense of the word, but I think that they do fall into the range that we see in interventional neuro.

Yes, Dr. Brem?

DR. BREM: Is the concern for the radiation exposure to the patient or the concern for the practitioners, because the patient, it seems the risk/benefit ratio is weighted in their favor. I think the concern perhaps on the warning should be for the people in the room doing multiple

procedures.

DR. HURST: Yes, Dr. Richardson?

DR. RICHARDSON: Dr. Richardson. I'd just like to ask if the age of the patient is a critical factor in that. I mean, a young patient I would be very concerned about that long of exposure, but in someone my age, I wouldn't be concerned at all.

DR. HURST: I think that's absolutely right. And when we work on pediatric cases, at least in my experience at Children's Hospital, they have their own dose rates and doses that are monitored there. So, absolutely, in a pediatric population, those doses are different.

Yes, Mr. Mueller?

MR. MUELLER: Yes. Dave Mueller. I believe during the Sponsor's presentation, they made the statement that the actual use of the PED wasn't the delay of the longer time. It was finding the outflow at the other end of the -- you know, trying to find where is the actual outflow of the artery. So I'm not sure it's, you know, related to the reasonable assurance of safety for the PED when it's trying to find an outflow for whichever procedure you're going to be doing in that patient.

DR. HURST: Yes, Dr. Eydelman?

DR. EYDELMAN: Actually, that's not correct because the device description inherently -- its utilization. But irrelevant. The question remains as is.

DR. HURST: Yes, Dr. Richardson?

DR. RICHARDSON: I think we need to keep in mind that we're dealing with a potentially fatal disease and the risk factors are in proportion to the risk [sic]. If I had an aneurysm this size, I would take pretty much any risk to get it treated, and I think most patients will, too. That doesn't mean we shouldn't be concerned about the side effects, but to terminate a procedure based on radiation time in someone with a fatal lesion is a physician's call.

DR. HURST: Thank you.

Any other comments?

(No response.)

DR. HURST: Then let me be sure I have the question. So I think the sense of the Panel is that the observed fluoroscopy exposure times and adverse events do support a reasonable assurance of safety for the PED based on that.

DR. EYDELMAN: Thank you.

DR. HURST: Question No. 3?

DR. HUTTER: In the PMA study, only limited use of ancillary devices (22 balloons, 1 coiling) was observed. The proposed labeling has no warnings or precautions regarding concomitant use of ancillary devices. Do you believe that specific labeling warnings or precautions are warranted for the PED?

DR. HURST: Dr. Ku?

DR. KU: I think based on the material that was presented, including the supplementary information from other studies, that probably this is a physician-determined practice, and so I personally don't feel that a specific warning is warranted other than sort of a general warning that, you know, if you're using another device, that the operator obviously should be aware of the pros and cons and the risks and benefits of the other device in addition to the use with this particular device.

DR. HURST: I would agree with that. And I think that there was a comment made during the Sponsor's presentation regarding a potential answer or addition to the IFU with respect to the use of additional devices should essentially be at the discretion of the treating physician. And I think that would be my input as well.

Other comments from Panel members?

(No response.)

DR. HURST: Then I think that the sense of the Panel is that there would be no need for specific labeling, warnings, or precautions warranted.

DR. EYDELMAN: Thank you.

DR. HURST: At this point, I think we're about probably in a position to break for lunch.

Let me just remind all the Panel members, as we do break for

lunch, to please not discuss the meeting during lunch amongst yourselves or with any member of the audience. We'll reconvene at 1 p.m. Please take your personal belongings with you. The room will be secured by FDA staff during the lunch break, and you will not be allowed into the room until we reconvene.

Thank you.

(Off the record at 11:45 a.m.)

A F T E R N O O N S E S S I O N

(1:00 p.m.)

DR. HURST: And we'll now proceed with the Open Public Hearing portion of the meeting. Public attendees will be given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda.

Dr. Claudio will now read the Open Public Hearing disclosure process statement.

DR. CLAUDIO: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the Open Public Hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have such a financial relationship. If you choose not to address this issue of financial relationships at the beginning of your statement, it will

not preclude you from speaking.

You will have five minutes for your remarks. When you begin to speak, the green light will appear. A yellow light will appear when you have one minute remaining. At the end of five minutes, a red light will appear and the microphone will be cut off. Since we have a number of speakers, it is very important to adhere to the five-minute time limit.

As each speaker concludes their remarks, Ms. AnnMarie Williams will guide the next speaker to the podium.

The Panel will be given an opportunity to ask questions to the public presenters at the conclusion of the Open Public Hearing. If recognized by the Chair, please approach the podium to answer questions.

Dr. Hurst?

DR. HURST: We have had eight requests to speak. We ask that you speak clearly into the microphone to allow the transcriptionist to provide an accurate record of this meeting.

Ms. Christine Padget, will you please approach the podium?

MS. PADGET: Good afternoon, ladies and gentlemen. My name is Christine Padget, and I'm a recipient of the Pipeline Embolization Device. I would like to thank Chestnut Medical for reimbursing me for my trip to speak to you today.

On April 27th, 2009, I developed what I thought was just another migraine. When the pain in my head became so severe that I

couldn't keep food down, I couldn't keep water down, and I couldn't sleep for days, I went to my local ER and told them all of my symptoms. I was sent home with no pain medication.

On the third time back to my local ER, they were going to send me home again, and my husband, my hero, told them, "You're not letting my wife out of this hospital until you run tests." That is where my miracle began.

At that time, they did a contrast CT scan, and it showed something leaking into my brain. I was taken by ambulance to Sutter Roseville Hospital in Sacramento, California. While there, I had two seizures and collapsed unconscious. The ER doctor did more tests. The results showed I had a giant aneurysm on my carotid artery behind my left eye in my brain.

I was in critical condition and the aneurysm could rupture at any time. The ER doctor said if I didn't have surgery, I could have multiple strokes or even die. He then told my husband about Dr. David Fiorella at St. Joseph's Hospital in Phoenix, Arizona, who was doing an investigational procedure called the Pipeline Embolization Device. The ER doctor called Dr. Fiorella and told him all about my case. Dr. Fiorella said, "If you can get her here, we'll save her."

We waited three days for our insurance to finally approve me to be life-flighted to Phoenix. I was brought to the ICU and stabilized. On

May 8th, 2009, I underwent the Pipeline surgery. The procedure took about 27 minutes. They didn't have to cut my head open. They made a small incision in the artery on the right side of my groin. I woke up in recovery about 5 a.m. the next morning, hungry for something to eat because I hadn't ate for at least ten days. Within minutes, my husband said I let out a shout, my eyes rolled into the back of my head, and I passed out.

Thankfully, my doctors were in the hospital, and Dr. Fiorella figured out I was bleeding internally. They rushed me back into OR and did an angiogram and found another aneurysm on my splenic artery, and it had ruptured. Dr. Fiorella then closed the artery using a coil. Again, Dr. Fiorella saved my life.

Four of my nerves in my brain were damaged by this aneurysm. My left eye was paralyzed shut, my vision was distorted, but now, almost two years later, my left eye is doing better. I still have some problems with my sensation in my up and down movement.

I'd like to thank God, my doctor, and the Pipeline for the greatest gift that could ever be given, life. Without the Pipeline, I would not be standing here speaking to you today. It is my hope and my prayer that you will approve this Pipeline procedure so that other people will be given the same second chance at life that I was given.

I also have five more aneurysms in my body that my doctors are watching. It is also my hope and prayer someday I will be able to get

those aneurysms fixed by the Pipeline.

I also have no side effects from this procedure, none. The issues that I'm dealing with with my left eye are as a result of the damage that was done to my nerves.

Thank you very much for your time.

DR. HURST: Thank you, Ms. Padget.

Jennifer Kabaci?

MS. KABACI: Good afternoon. My name is Jenny Kabaci. I'm 46 years old. I live in Arizona, and I'm a recipient of the Pipeline device. I'd like to thank Chestnut Medical for reimbursing me for my trip to speak to you today.

A little over a year ago, I started getting a bad headache. Over a period of three days, it got worse, and my vision became doubled. I could barely walk across a room, let alone drive my kids to school or take care of a household.

I called my husband at work and told him how bad it was, and he came home and took me to urgent care. The urgent care doctor immediately sent me to the hospital.

At this point, I was thinking that maybe it was just a really bad migraine or a sinus infection, but the CT scan showed that I had a 3-centimeter mass in my brain. I don't think there is any way to explain the feeling of utter fear and panic that swept through my whole body. It was

like an indescribable wave of heat that ran from the top of my head to my feet. My first thoughts were that I had cancer. An MRI showed that it was an aneurysm. I had heard of aneurysms, but that was something that happened to other people, not me.

The results of the MRI were sent to the Barrows Institute in Phoenix, where Dr. McDougall reviewed them. Dr. McDougall immediately agreed to take me into his care. At once, I was taken to Barrows, and it was there that I got a crash course on aneurysms. My aneurysm was categorized as a giant, wide-necked aneurysm. Dr. McDougall explained to me my options for treatment, the standard options like coiling and surgery. They didn't look good. Then Dr. McDougall explained the Pipeline device to me. He drew a picture of my aneurysm and showed me how the device would work. It seemed like the miracle I was hoping for. Only one thing stood in the way: the Pipeline was not FDA-approved yet.

Dr. McDougall and his team worked diligently on my behalf to get access to Pipeline for emergency use. It took about a week, but my miracle came true. The hospital agreed to the surgery. Chestnut Medical provided the Pipeline devices and technical support, and the FDA granted approval for the one-time use of the device. Almost like a dream come true, I had hope again.

So on January 14th, 2010, just seven days after originally going to the urgent care, I had my surgery. Two Pipeline devices were used for my

aneurysm, and I was able to go home within three days of surgery.

In the days following the surgery, I still had double vision and the headaches, but in about four months, as the blood flow to the aneurysm was reduced, the double vision, for the most part, went away. Today, the headaches are less frequent and less severe. For the most part, I've been able to resume my life. I can once again drive my kids to school and do all the other day-to-day activities of my life.

I am living proof that Pipeline works. Without the option of Pipeline, I don't know where I would be today. I'm thankful for the people at Chestnut Medical for providing these medical devices. Now, when I hear about somebody having an aneurysm, I think to myself, I sure hope they have the option of Pipeline. I strongly urge the FDA to approve the Pipeline Embolization Device. Countless numbers of people will surely benefit from it. I know that I have.

In summary, prior to my treatment, I couldn't see and I had extreme head pain. As a mother and a wife, I was virtually ineffectual. But here I stand today a year later, and I have most of my life back. My vision is mostly back. I can drive, shop. In short, I can take care of my family, and I owe it all to the folks at Chestnut Medical, to Dr. McDougall and his staff at Barrows, and the FDA. The speed at which the Pipeline device was approved and installed is the reason why I can stand here today and share my story.

So I'll close by saying thank you from the bottom of my heart

for all you've done for me. And please approve this device so that others like me will have a chance at a better life.

Thank you.

DR. HURST: Thank you.

Next is Ms. Susan Sims.

MS. SIMS: Hi. I'm Susan Sims from Atlanta Georgia, and I want to thank Chestnut Medical for reimbursement to be here today, and I especially want to thank all my doctors and the people who had the ability to make this Pipeline, because if it were not for the Pipeline, I would not be here today. I know that in my heart.

I was diagnosed two years ago, in 2007 -- I had -- I was 52. I was having double vision, headaches, dizziness, but the worst pain was the pain I felt in my ear, around the rim of my ear and the back of my head. It was so excruciating, sometimes I couldn't hardly tolerate it.

I actually went to the doctor for a lump in my neck that I had found and thought these symptoms might be from that. He sent me for an MRI. The MRI showed the lump was nothing, but there was another problem. I had a very large aneurysm. He told me he thought the symptoms were from the aneurysm.

I was sent to see Dr. Cawley and told the only place I could really be treated in Georgia was Emory Hospital. Unfortunately, the only thing they could do was coiling or Onyx. The Pipeline wasn't available there.

But I had found some information on the Internet about the Pipeline myself.

And the day that I was scheduled for my operation for the coiling procedure, Dr. Cawley called me in to discuss the Pipeline with me. He said he felt this was the perfect fix for me. And after going through a balloon occlusion and knowing I might have to sacrifice the artery, I knew I didn't want that. He told me this could be a cure for me, and it has been.

I had the Pipeline two years ago, and on my year checkup, the aneurysm was gone, and I thank God for that. And I hope and pray that this will be passed because there are so many people out there that need this Pipeline, and it can help them. And I just hope and pray that it will be passed.

Thank you.

DR. HURST: Thank you.

Christine Buckley?

MS. BUCKLEY: Good afternoon. My name is Christine Buckley, Executive Director of the Brain Aneurysm Foundation, a nationwide non-profit focused on providing support, awareness, educational materials, and research funding for brain aneurysms. I'd like to thank Chestnut Medical for providing my travel costs.

I am here to represent brain aneurysm patients, the consumer and their families. Brain aneurysms are a devastating disease, not only to the individual affected, but also to the families. Brain aneurysms can lead to

strokes, severe disabilities, and death. On a daily basis, the foundation talks to patients each day with various scenarios, questions, and concerns.

The worst scenario for me or my co-worker to deal with is when a patient calls to say they were told by their doctor there is no effective treatment for their aneurysm, and one such example of this is a patient that has a large or giant aneurysm that cannot effectively be treated by clipping or coiling but could be helped by Pipeline.

The availability of the Pipeline device will be a great breakthrough in aneurysm treatment for many patients who otherwise would have no treatment options, and it will give these patients, as you have heard so far today, a new start on their life and also their families' as well.

As with any surgery, there are risks, but based on the results of PUFS, the trial, and discussions with the many members of the foundation's Medical Advisory Board, I have learned that this new technology will be welcomed as an option for treatment and a breakthrough for those diagnosed with a large or giant aneurysm.

As executive director of the only non-profit organization that is serving the needs of brain aneurysm patients, I look forward to the day that I can announce to the patient population that we serve, our supporters and their families, the availability of Pipeline as a method of treatment for the appropriate patients that would otherwise be left untreated or ineffectively treated.

Thank you very much.

DR. HURST: Thank you.

Tanya Wuchner, please?

MS. A. WUCHNER: Good afternoon, ladies and gentlemen. My name is Amanda Wuchner, and this is my mom Tanya. We are here from Humboldt, Saskatchewan in Canada, and we would like to thank Chestnut Medical Technologies for helping us be here today.

I was treated for a brain aneurysm with the Pipeline Embolization Device in April 2008. We'd like to briefly tell you how that came about. I began getting headaches when I was about 12 and a half years of age. At first, they would only last a day or two and it happened once every month or two. I took over-the-counter medications like acetaminophen and ibuprofen and that would help.

After several months, they began to get worse. It happened more often and lasted much longer. Medications would not help relieve the pain, which was usually on the back left side of my brain. I also started to have severe upper back pain and neck pain, which often made it difficult to turn my neck or to sleep at night. Occasionally, I would get ocular migraines, which are disturbances in the peripheral vision.

MS. T. WUCHNER: Amanda was sent for a CT scan in January of 2008. The scan showed that, the presence of a giant midbasilar aneurysm. A neurosurgeon viewed the scan results and told us about the

options, one, invasive surgery to clip it, two, endovascular surgery using coils and a stent to block it or, three, do nothing. He informed us that the location of her aneurysm made invasive surgery virtually impossible. He also said that there is a much greater risk of rupture with giant aneurysms, and the outcomes were not good. There could be severe complications or death.

So leaving it was not an option for us. She was referred to another medical facility out of our province to try and have endovascular surgery done with coils. An attempt was made there to repair the aneurysm, but the surgery was stopped before any coils or stent were deployed. Due to the blood flow within the aneurysm, the coils were not reacting the way they were supposed to. They were floating up to the top of her artery instead of settling down into the aneurysm. Since the outcome was not certain if the procedure continued, it was aborted. We were told there was nothing else that could be done and to come back in six months for an MRI to see if there was any changes.

We were devastated, to say the least. We returned home and decided to see if there was anything else that could be done. We were put in contact with Dr. Michael Kelly and Dr. David Fiorella who were working at the Cleveland Clinic at this time. They had used the Pipeline Embolization Device successfully in two other patients and believed that it could help Amanda. They sought permission from the FDA, Chestnut Medical Technologies, and the Cleveland Clinic to treat Amanda and were granted it.

We traveled to Cleveland from Saskatchewan, and on April 11th, 2008, Amanda had endovascular surgery at the Cleveland Clinic, using the Pipeline Embolization Devices to repair her giant aneurysm. The procedure was successful. She was only in the hospital for three days, and testing five days after the surgery showed that the aneurysm had been completely blocked, with no blood flowing into it.

We returned home back to Saskatchewan one week after the surgery. One year later, these are the follow-up pictures.

MS. A. WUCHNER: It's been three years since the surgery, and I'm doing great. I was really happy to have the aneurysm fixed and get rid of all the headaches, back and neck pain, and vision problems. I haven't had anything like that since we came back home. At first, I couldn't play all the sports I used to because I was taking aspirin and Plavix, and there was a risk of bruising and bleeding, but I continued to do low-impact sports like cross-country running, track and field, and badminton. This past summer, I was able to quit taking Plavix, so now I'm doing everything I used to. This fall, I played outdoor soccer and competed in cross-country running. I just finished up our indoor soccer season, and I'm playing with my high school senior girls basketball team. I play the piano and maintain an A-plus average at school.

DR. EYDELMAN: You have 30 seconds.

MS. A. WUCHNER: I'm very grateful to Chestnut Medical

Technologies for developing the Pipeline Embolization Device and for giving Dr. Fiorella and Dr. Kelly permission to use it, because it saved my life.

Thank you.

DR. HURST: Thank you.

Dr. Christopher Moran?

DR. MORAN: Good afternoon. I'm Dr. Christopher Moran. I'm a Professor of Radiology at Washington University in St. Louis. I have a joint appointment in the Neurological Surgery Department. We treat roughly 150 aneurysms a year, endovascularly, and we treat another 100 aneurysms with open surgical techniques.

As a way of disclosure, I am a consultant for ev3. I proctor, I speak, and they have also paid my travel expenses and lodging this particular time.

So what I'd like to do is speak on behalf of three different groups. I thought the third group was going to be the easiest or the hardest, but looking at the people who have already spoken, I shouldn't speak for that group. They've spoken for themselves.

But what I would like to do is give you the perspective of someone who uses the device and has used the device, and also, the perspective of the American Society of Interventional and Therapeutic Neuroradiology, which is now the Society of Neurointerventional Surgery, which is an organization of 600 physicians, interventional neurologists,

interventional neurosurgeons, and interventional neuroradiologists who have come together to treat people endovascularly with these very, very difficult lesions. Our goal is to be able to treat these patients safely, effectively, and have the research to prove that it's indeed effective.

So what are we trying to do? Well, in the past, we were trying to fill the aneurysm and thereby reconstruct the neck and reconstruct the parent artery. If you fill the aneurysm, the blood couldn't get to the weak spot. We had several different devices, balloons, which are approved, and stents, which only have HDE and HUD approval, and liquid agents such as Onyx HD500.

This is an example of those devices, and I think an important thing is to look how that Pipeline that you've seen several different times today, how flexible it is. You can tie it in a knot. If you look at the devices on the left side of the screen, those stents, while they're somewhat flexible, nowhere near the flexibility. So some of those aneurysms remain very difficult to treat.

What happens when you place these devices? Well, it's a little different than what we did before. We filled the aneurysm. Now, what we're relying on is the mechanical effect of the Pipeline device to keep the blood from getting in and getting out of the aneurysm. When that happens over the next several days, the blood sits there, and it wants to clot. And then after it clots, fibrous tissue forms, and fibrous tissue and endothelial

cells grow along the wall of the blood vessel. And then what that enables to happen is the vessel is healed, the aneurysm is excluded from the circulation and can no longer bleed.

I'm also going to speak a little bit as a practitioner. And I have placed the device in four different patients. One of the patients lost hair. It was only 60 minutes of the fluoro time. It was very difficult. And we test our fluoro equipment every quarter to make certain that it doesn't emit too much radiation.

The other thing as a practitioner, when we hear about the aspirin and Plavix, I looked at a study that I did some years ago, 12% of our patients developed groin hematomas just with diagnostic arteriography. So it's a very sensitive thing. Just think about it. You're poking a hole in the artery, and it leaks along.

This is the patient that I wanted to show. This is a 32-year-old man who I had seen ten years previous. He was disabled by headaches, narcotics all the time, pain relievers all the time. He could have no job. He finally found a job about four years later when he was able to get off the narcotics, but he was found to have this aneurysm. This is a siphon aneurysm. It extends into the ophthalmic segment. It has calcium in it, and it's an impossible aneurysm to treat.

With the Pipeline, we were able to place devices across it, slow the flow, and this is what he looked like ten months later. He was also one

of the patients, because I couldn't get him back, because he finally had a job and he didn't want to come back because he was worried about losing his job -- he wouldn't come back to St. Louis to get his arteriogram. So he would be one of the people who actually failed according to the definition. But when you look at that, that aneurysm isn't failed. It's cured. That vessel is now widely patent. His headaches are gone, he's back at work --

DR. EYDELMAN: You have 30 seconds.

DR. MORAN: When I did the arteriogram and I was standing over him, he grabbed me and gave me a hug when I told him he could get on with his life. And I thought he was just a little disinhibited because of the medications that we gave him. I went to see him a little bit later, and he said, "Can I give you another hug?" And I said, "Absolutely." So this needs to be approved to help us take care of our patients. Thank you.

DR. HURST: Thank you.

Ruth Nicholson?

MS. NICHOLSON: Hi. My name is Ruth Nicholson, and this is my husband Rob. We're from Green Bay, Wisconsin. First, I would like to thank Chestnut Medical for reimbursing us for food, travel, and lodging so we can be here today to tell you about our experience with the Pipeline Embolization Device.

For more than two years, I had headaches, neck pain and tightness, along with occasional visual disturbances which consisted of no

left peripheral vision and floaters. My head felt like a ton pushing on my neck, and I would develop throbbing pain in the right base of my skull especially with exercise. Massage and chiropractic care didn't help. After much encouragement by my husband, I went to the doctor. She started me on nortriptyline for possible migraines and sent me to physical therapy, which, too, did not help; then tried traction. That made it worse.

Finally, they ordered an MRI, which showed a large aneurysm in my right vertebral artery. I was directed to a neurosurgeon who introduced us to Dr. Lev, an interventional radiologist, at Aurora Hospital in Green Bay, who performed an angiogram February 22nd, 2010.

My husband remembers her saying, "You're one in a million," and she did not mean in a good way, and that I have fibromuscular disease. I remember her saying, "I wish I had better news," and then telling me to fill out my five wishes. I'm a hospice nurse. I knew what that meant. I think Dr. Lev wanted to gather all of her information before telling us our options. So the waiting began.

Before we left the hospital, she said, don't exercise, avoid golfing, and recommended we do not fly to Mexico as we had planned for the following week, and to avoid stress. Don't stress? How could we not? The risk of rupture was pretty high, so I was afraid to be left alone, and every little pain or pressure would scare me. I did not want to die or become incapacitated and be a burden on my family.

We canceled our trip, and with multiple conversations about stenting, coiling, resection, clipping, and why they wouldn't be the best option, time seemed to move very slowly, and an answer seemed so far away.

Dr. Lev talked about the PED and was still researching our options. We went to see Dr. Agard Kenitz (ph.) at UW Madison for a second opinion. She indicated the same thing. Pipeline is the best option. Dr. Lev's call came, and we were able to get the Pipeline placed, but I was not a candidate for the clinical trial. The options were Canada or Argentina. Since I couldn't fly, Canada with Dr. Morada (ph.) was our answer. But more waiting for the procedure day to be scheduled.

My husband called a friend who was a physician in Canada for some recommendations on comfort, I think. He highly recommended Dr. Morada in Toronto, as did Dr. Lev and Dr. Agard, but we still had to wait for Dr. Lev and Dr. Morada's office to arrange everything.

Finally, we got the word that Dr. Morada, at St. Michael's hospital in Toronto, Canada, would place the device. Monies were wired, and then another week went by before we got the word to go. This was the end of March. We literally dropped everything and started our drive to Toronto.

Everything went well. I spent two days in neuro ICU, two days on the neuro floor, spent the weekend at the hotel just in case. Easter

Sunday, we were headed home.

Seven months after the device was placed, the follow-up angiogram looked perfect. I still would get scared when my heart rate went up, like now, but the headaches were gone.

Now, 12 days before the year mark, I'm gradually working my way back to my prior exercise routine without the throbbing in my head or neck and have not had the pain like before. I am still taking Plavix and aspirin.

Looking back on the whole ordeal, I remember that initial shock, then the worries and fears about the aneurysm itself, and then the additional stress related to going out of the country for the procedure. Even though the Toronto medical staff was great, I do not wish that extra burden upon anyone else.

Because of my FMD and the small blisters on some vessels, the Pipeline may be needed in my future again, and I would much prefer to have the procedure done at home in the United States. We're especially grateful to Drs. Morada, Raisa Lev, and Dr. Agard Kenitz for making my Pipeline treatment available.

And thank you for your time.

DR. HURST: Thank you.

Ms. Robin Burruss?

MS. BURRUSS: I'm actually Penny Burruss. Robin is my

husband. Good afternoon. My name is Penny Burruss. I'm a 59-year-old wife, mother, and grandmother from Marietta, Georgia. First of all, I wanted to say that we were offered assistance from Chestnut Medical for travel, lodging, and food expenses, but we declined.

As I'm not accustomed to public speaking, please allow me to read my prepared statement. I'd like to thank the FDA for the opportunity to give testimony before you today concerning my experience with the Pipeline procedure. In June of 2009, I was suffering from a sinus infection and went in to see my family physician with hopes of getting a referral to a specialist that could help me with these frequent infections. She suggested that I have a sinus CT first.

The next morning I had the CT scan, and that afternoon, she called me back into her office to discuss the results. That is when she revealed to me that I had a brain aneurysm. It was hard for me to believe because I had no symptoms to even suggest I had a problem of this nature. No headaches, no vision problems, nothing. An MRI a few days later confirmed this devastating news.

I had five young grandchildren and two more on the way. After 37 years of marriage, my husband and I were finally making plans to retire and enjoy the fruits of our labors. Suddenly, the reality crashed in on me. These thoughts filled my mind: How much longer do I have with my husband, my children, and my grandchildren? Who is going to take care of

my mom with Alzheimer's and my 84-year-old dad who lives alone and my handicapped sister? Will I never get to see those places I've longed for and waited to see?

I was referred to Dr. Daniel Barrow, Chief of Neurology at Emory Hospital in Atlanta. After an angiogram, Dr. Barrow discussed with me the gravity of my condition. He described my aneurysm as large and complicated. Visually, it looked like a snake that had swallowed a large object, distended all around instead of off to one side. He shared with us some methods for dealing with aneurysms. One, do nothing, but the probable outcome could be devastating; clipping or coiling, but because of the shape and size of my aneurysm, that was not an option.

Then he proposed a third possible option, the Pipeline, a new procedure he knew about that was being performed in clinical trial at New York University Medical Center. As he described the procedure, I suddenly felt there was hope for me. I remember the excitement I felt with this possibility. I could hardly contain myself when he told us that he had already contacted Dr. Nelson and Dr. Becske and had sent my results to them. They responded that they thought I would be a good candidate for this procedure and even tentatively reserved a surgery date pending approval from the FDA and myself.

Suddenly, there was hope that something could be done to prolong my life. There was no doubt in my mind that this is what I wanted

to do, so we began preparations for our journey to New York. Within a few weeks, we were on an airplane headed to New York. On final approach, I experienced a strange sensation in my head that startled me but lasted only a couple of minutes. Though it had come and gone, I felt I needed to mention it to the doctors before my surgery.

The angiogram done during my surgery revealed a new bulge on the aneurysm itself that had not shown up on the angiogram in Atlanta only weeks earlier. Was the event on the airplane the near rupture of the aneurysm? We will never know for sure, but something happened on that airplane.

The surgery was a complete success, and I returned to Atlanta. I felt I had my life back. I have now resumed all the previous activities I had enjoyed prior to this surgery, walking, golf, tennis, and best of all, playing with my seven precious grandchildren.

I view the Pipeline as a godsend. Thankfully, it was available to me when I needed it, just in the nick of time. I don't believe that was a coincidence. I want to express my sincere appreciation to you, the FDA, for making it possible for me to receive this Pipeline procedure. Special thanks to my wonderful doctors, Dr. Nelson and Dr. Becske, for their skilled hands and compassionate hearts in performing my surgery. And, finally, thank you Chestnut Medical for pursuing the development of this life-saving device. I am forever indebted to all of you. I believe Pipeline saved my life.

I would like to strongly recommend to the FDA to give full approval for the Pipeline so that many others faced with this same dilemma can have a chance to continue their life with their loved ones, as I have.

Thank you so much.

DR. HURST: Thank you.

Does anyone else wish to address the Panel at this time? If so, please come forward to the podium and state your name and affiliation and indicate your financial interest.

(No response.)

DR. HURST: Does anyone on the Panel have any questions for any of the speakers?

(No response.)

DR. HURST: Okay. This session of the Open Public Hearing is now closed, and we'll now proceed with today's agenda.

At this time, we'll continue to focus our discussion on the FDA questions. Again, copies of questions are in the Panelists' folders, and I'd ask each Panel member to identify him or herself each time he or she speaks.

Dr. Hutter will again present the FDA questions. Dr. Hutter, please read the fourth question, I believe it is.

DR. HUTTER: In 5 out of 50 cases performed using the Renegade Hi-Flo microcatheter for PED delivery, the physician experienced

excessive friction when trying to pass the delivery wire through the microcatheter. No such cases of excessive friction were reported for the 55 cases with the Chestnut Marksman microcatheter. However, the proposed labeling allows for the use of any microcatheter with a 0.027-inch diameter. Should delivery of the PED be limited to:

a. Chestnut Marksman, or

b. Catheters used in the IDE study, or

c. Any catheter with a 0.027-inch inner diameter?

DR. HURST: Dr. Ku?

DR. KU: Dr. Ku. As a active practitioner who has placed other types of intracranial stents, I feel that the latter should be the preferred choice, where the physician can make the decision to pick the type of catheter. Part of the reason is that technology advances all the time, and if you limit it to a single catheter, you may wind up with a catheter which is superior, and if it's restricted, you may be precluded from using the device based on medical/legal reasons rather than true efficacy reasons. So I would suggest that any catheter with the appropriate diameter should be available.

Now, obviously, most practitioners who would be using the device probably at the current stage would be smart enough to use the catheter that has the least amount of friction. So it's kind of a intuitively obvious answer.

DR. HURST: Yes, Dr. Yang?

DR. YANG: Lynda Yang. I would again ask the interventionalists on the Panel, is a 10% rate of encountering friction something that you would normally see or is that less than or more than?

DR. KU: It depends on the tortuosity, how many turns do you have. A lot of it depends on the acuity. And it also depends on where the turns are as to where the friction points are. So you may have a vessel in the carotid that's not a problem, but because of proximal tortuosity, you'll get the resistance lower down, and you won't be able to deliver the force distally. So it's very, very variable.

DR. HURST: I would certainly agree with that, that to a large extent, that's going to depend on the tortuosity of the vessel that you're using. And I also agree that to leave the physician, the operating physician the leeway to use any catheter appropriate rather than to just specify a particular catheter is probably a wise decision.

Other comments?

Yes, Mr. Mueller?

MR. MUELLER: Yes. Dave Mueller. I just wanted to point out again, as it was mentioned earlier, that it's not 5 out of 55. It was 5 out of 60, because when they had the ones that were friction, they removed it and used the same catheter back again, and it worked.

DR. HURST: Thank you.

Dr. Eydelman, I think the sense of the Panel is that the

catheter should be appropriate for use with any appropriately sized catheter rather than specifying a particular brand or model of catheter.

DR. EYDELMAN: Thank you.

DR. HUTTER: The proposed indications for use statement reads, "The Pipeline Embolization Device is indicated for endovascular treatment of large or giant wide-necked intracranial aneurysms in the cavernous and paraclinoid regions of the internal carotid artery." Do you believe that modifications are warranted with respect to:

a. Age (youngest appropriate age)

b. Ruptured vs. unruptured

c. Anatomic locations, and/or

d. Other considerations?

DR. HURST: Comments from the Panel?

Dr. Ku?

DR. KU: Addressing the first point, age, I don't -- I think the proposed indication 21 and above is reasonable. Obviously, you've heard that patients younger than that have been treated, and that, obviously, I think should be at the discretion of the physician. Giant aneurysms are potentially lethal with a relatively high percentage of rupture or development of significant clinical symptoms. And so that has to be weighed against, you know, operating on a patient who's young.

Number two, ruptured versus unruptured, use of antiplatelet

drugs is a major problem in patients with acute ruptured subarachnoid hemorrhage. The incidence of complications increases severely, but if you are dealing with a lethal or a near lethal condition such as a ruptured aneurysm, it basically is dependent on the clinician as to whether they really need the device or not. They have to balance the risks of febrile bleeding with use of antiplatelets versus whether they really need the device. There are many strategies that are available, such as partial treatment of the aneurysm with other modalities, such as partial coiling; then waiting for an appropriate number of days, typically, four weeks, because usually the aneurysm has stabilized in four weeks and you can give antiplatelet drugs relatively safely at that point. And I guess the one case where the manufacturer or the Sponsor indicated that a patient had a ruptured aneurysm treated within less than 60 days, I'm assuming that's probably the situation, where they must have done a partial treatment and a delayed stent placement, but I can't speak to that.

Location. For the proposed locations, I think the indication is appropriate. They've done the background work and the clinical testing to show that it is a reasonable -- it's reasonable to approve it for their specific locations. And that's about it.

DR. HURST: Other Panel members' comments?

DR. BREM: I'm just wondering whether we should consider eliminating the age restriction because it's relatively rare in younger people.

I think it puts an onus on the treating physician that they're going against recommendations to use it, but there are still no good options for those children. And, you know, we had a very dramatic example of that today, where it's life-saving. I don't know why -- I understand why we would put it in, because the study was done in adults, but I would be in favor of just eliminating the age restriction or not discussing the age restriction.

DR. HURST: Other comments?

(No response.)

DR. HURST: I would kind of go along with that. I think that, as Dr. Brem mentioned, most of these intracranial aneurysms, certainly well over 98%, are going to occur in the age 18 and above. Again, I don't want to get into an administrative problem in that there was no pediatric population looked at, whether that might raise a problem. I'm not sure that there needs to be an age restriction on the device either.

Yes, Dr. Richardson?

DR. RICHARDSON: We've heard two patients who were used off label today, so what is the status of using it for basilar artery aneurysms?

DR. HURST: I can let Dr. Eydelman address that, or I mean, my sense would be that these were compassionate use. Is that a correct understanding? That's why they -- they were used outside of the trial as a compassionate use?

DR. RICHARDSON: What's the status of having it approved for

basilar artery aneurysms? Does that require another complete study?

DR. EYDELMAN: Well, today, we're here to discuss the proposed indication that the Sponsor is currently proposing. As you see, that is not part of the current indication. If the Panel wishes to make some kind of recommendations, should the Sponsor choose to come for that indication in the future, we'll take Panel's considerations into our assessment.

DR. RICHARDSON: That's why I asked the question. Do we need to make a recommendation regarding use of -- it's classically -- an obvious indication for the use of the device is midbasilar aneurysms.

DR. HURST: I mean, I think that if it were approved for one indication, use of it as an off label indication would certainly be a reasonable consideration for a basilar aneurysm.

DR. EYDELMAN: Yes.

DR. HURST: In other words, I don't think that we're -- we would be depriving anyone with a basilar aneurysm of having access to this device if the labeled indications said the paraophthalmic aneurysm, as they do now.

DR. EYDELMAN: I'm sorry --

DR. HURST: We just continued discussing a little bit the potential for use of it as an off label indication if it were approved, that this would not prevent the use, for example, in a basilar aneurysm.

DR. EYDELMAN: That's correct. Once it's on the market, it's up to the physician's discretion.

DR. HURST: Yes. Dr. Yang?

DR. YANG: I was just wondering if that's something that could be looked at in the post-approval study?

DR. EYDELMAN: No. Post-approval study is usually to further assess indications that were approved.

DR. HURST: Anybody have any other comments?

(No response.)

DR. HURST: Then I think the sense is that there really don't seem to be the requirement for any modifications of these indications.

UNIDENTIFIED SPEAKER: Except for age?

DR. HURST: I'm sorry, except the potential -- except for age.

DR. EYDELMAN: Thank you.

DR. HUTTER: In light of the proposed post-approval study, please address the following questions:

a. Does the primary endpoint adequately capture the safety concerns associated with the device?

b. Is the proposed safety threshold of less than 25% for the primary endpoint of ipsilateral stroke and neurovascular death appropriate?

c. Are there other subgroups in addition to the two proposed anatomic subgroups that are important to consider for performing

statistically powered analyses?

DR. HURST: Dr. Ku?

DR. KU: Dr. Ku. The primary endpoint seems to be well met, based on the p-values that were demonstrated, and the safety threshold of less than 25%, I think, is based on a relatively good estimate -- previous historical data. And I'd probably defer to our statistician as to whether there are any other subgroups that might be considered. I don't have any particular issue.

DR. HURST: Thank you.

Dr. Posner?

DR. POSNER: Dr. Posner. This is just a question based on information from the FDA, where they did find a difference in the hypertensive subgroup seem to have a higher incidence of neurological events and wondered whether they wanted to consider a hypertensive subgroup in the post study.

DR. EYDELMAN: We look forward to Panel's thoughts on that subject.

DR. HURST: Anyone else have any comments regarding the post-approval study?

Yes, Mr. Mueller?

MR. MUELLER: Dave Mueller. I'm sorry. Not on this one, but I wanted just to ask the Chair's clarification on the previous one regarding the

labeling. Regarding age, was that to say to, yes, add an age requirement or no age requirement?

DR. HURST: I think that the sense of the Panel was that we don't need to have an age requirement on there at all.

MR. MUELLER: Okay. Thank you.

DR. HURST: Okay. Other comments regarding the subgroup analysis or subgroups that might be -- right now, we have two subgroups in the PMA -- I'm sorry -- in the post-approval study, the supraclinoid and intraclinoid group. Adding a group of patients who are hypertensive was your suggestion. Any other comments?

DR. POSNER: Yeah. This is Dr. Posner again. On the hypertensive group, I think if they are going to do that as a subgroup, they'd have to look at controlled hypertension versus non-controlled. I mean, it would be -- they'd have to design the study so they knew what they were looking at.

DR. HURST: Um-hum.

DR. POSNER: And I would suggest they go back to the original data to see whether the neurological events in the hypertensive subgroup were those that were clinically hypertensive, or were they being treated for hypertension at that point. But I think it would be of interest to the people doing the study.

DR. HURST: Other comments?

Yes, Dr. Yang?

DR. YANG: Lynda Yang. I guess the other one I would think about would be peds versus adult if this device is approved.

DR. HURST: Thank you.

Dr. Eydelman, the suggestion was that we keep the same subgroups, perhaps adding a pediatric and a hypertensive subgroup.

DR. EYDELMAN: Thank you.

DR. HUTTER: Is there reasonable assurance that the PED is safe for use in patients who meet the criteria specified in the proposed indication?

DR. EYDELMAN: This is one of the voting questions, actually, so I think we're going to pause at this point.

DR. HUTTER: Okay.

(Off the record.)

(On the record.)

DR. HURST: At this point, we're going to take a 15-minute break. Let me just remind the Panel members not to discuss the meeting topic during the break amongst yourselves or with any members of the audience. And we'll reconvene here in 15 minutes.

Thank you.

(Off the record.)

(On the record.)

DR. HURST: And at this time, the Panel will hear summations, comments, or clarifications from the FDA.

MS. HOANG: Panel members, colleagues, ladies and gentlemen, I'm the Branch Chief of the Neurodiagnostic and Therapeutic Devices Branch, the group that oversees the review of this particular PMA, P-1000118, from Chestnut Medical Technologies for the Pipeline Embolization Device.

The following are our key summation points. The primary endpoint of major ipsilateral stroke and neurologic death were met, including analysis with worst case assumptions. We also found that the primary effectiveness composite endpoint of complete intraarterial occlusion without significant primary artery stenosis was met in the prespecified population and in sensitivity analysis. This effect was sustained through the one year.

Secondary independent endpoints were achieved at 180 days and sustained at the one-year angiographic evaluation. These endpoints are complete IA occlusion and parent artery stenosis.

The indication as proposed by the Sponsor raises concerns regarding age and terminology regarding the anatomic location. And in light of recent evidence of increasing rate of aneurysm recurrence and concern for the long-term risk of in-stent stenosis following the endovascular treatment, we found that one-year data provided critical support for the

safety and effectiveness of the device.

We very much appreciate the time that you've taken to discuss our questions.

Thank you.

DR. HURST: Any questions for the FDA personnel from the Panel?

(No response.)

DR. HURST: Does the Sponsor have any additional comments to make?

DR. CHER: Thank you. Daniel Cher. We have no further comments and thank the Panel for its time and consideration.

DR. HURST: Thank you. Before we proceed to the vote, I'd like to ask Dr. Gary Duehring, our Consumer Representative, Mr. David Mueller, our Industry Representative, and Dr. Phil Posner, our Patient Representative, if they have any additional comments.

Dr. Duehring?

DR. DUEHRING: I just have to compliment all parties involved, the vendors and the FDA staff, for an exceptional experience. And I would urge supporting approval.

DR. HURST: Thank you.

Dr. Posner?

DR. POSNER: This is Dr. Posner. I have to concur totally. This

has been very professionally run by the Committee, the presenters, and the FDA. It's been really good. And as a physiologist, I have learned a lot of physiology today, so it was educationally sound for me, too. And I urge approval.

DR. HURST: Thank you.

Mr. Mueller?

MR. MUELLER: David Mueller. I also want to thank the Committee and the FDA for a great job and the Sponsor for the great data, as well as all the patients and their families for coming and giving us their perspective. I too vote for -- would recommend the Panel to go ahead and vote yes.

DR. HURST: Thank you, Mr. Mueller.

We are now ready to vote on the Panel's recommendation to FDA for the PMA. The voting procedure has changed to an automated system. The Panel is expected to respond to three questions relating to safety, effectiveness, and risk versus benefit.

Dr. Claudio will now read three definitions to assist in the premarket approval application voting process. Dr. Claudio will also read the indication statement for the product.

DR. CLAUDIO: The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allows the Food and Drug Administration to obtain a recommendation

from an expert advisory panel on designated medical device premarket approval applications that are filed with the Agency. The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

The definitions of safety, effectiveness, and valid scientific evidence are as follows:

Safety, as defined in 21 C.F.R. Section 860.7(d)(1) - There is a reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

Effectiveness, as defined in 21 C.F.R. Section 860.7(e)(1) - There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Valid scientific evidence, as defined in 21 C.F.R. Section 806.7(c)(2) - Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials

without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

The Sponsor has proposed the following indication for use: As indicated for the endovascular treatment of large or giant wide-necked intracranial aneurysms in the paraclinoid region of the internal carotid artery.

The following questions relate to the approvability of the PED PMA P100018. Please answer them based on your expertise, the information you reviewed in your preparation for this meeting, and the information presented today.

The handheld remote will capture your vote after the question is read. For the next three questions, please press 1 to vote yes, 2 to vote no, and 3 to abstain. Please be certain of your response before you select your answer, as once the selection is made, there will be no opportunity to change your vote.

Before we begin, we will take a test vote to verify that the

voting devices are working properly.

I like the color blue.

Please press your selection, press 1 for yes, 2 for no, and 3 to abstain. As you vote, your name will disappear from the screen. Please lock in your vote.

(Pause.)

The poll is now closed.

Question 1 reads as follows:

Is there reasonable assurance that the Pipeline Embolization Device is safe for use in patients who meet the criteria specified in the proposed indication?

Please vote now. Please press 1 for yes, 2 for no, and 3 to abstain. As you vote, your name will disappear from the screen. Please lock in your votes.

(Pause.)

The poll is now closed.

We will now proceed to Question 2.

Question 2 reads as follows:

Is there reasonable assurance that the Pipeline Embolization Device is effective for use in patients who meet the criteria specified in the proposed indication?

Please vote now. Press 1 to vote yes, 2 to vote no, and 3 to

abstain. As you vote, your name will disappear from the screen. Please lock in your votes.

(Pause.)

The poll is now closed.

The third and final question reads as follows:

Do the benefits of the Pipeline Embolization Device for use in patients who meet the criteria specified in the proposed indication outweigh the risks of the Pipeline Embolization Device for use in patients who meet the criteria specified in the proposed indication?

Please vote now. Press 1 to vote yes, 2 to vote no, 3 to abstain. Please lock in your votes.

(Pause.)

The poll is now closed.

DR. EVANS: Find out about the color blue?

(Laughter.)

DR. CLAUDIO: I will now read the votes into the record.

For Question 1, is there reasonable assurance that the Pipeline Embolization Device is safe for use in patients who meet the criteria specified in the proposed indication, Dr. Yang voted yes; Dr. Ku, yes; Dr. Kang, yes; Dr. Richardson, yes; Dr. Becker, yes; Dr. Byrne, yes; Dr. Evans, yes; Dr. Brem, yes.

For Question 2, is there a reasonable assurance that the

Pipeline Embolization Device is effective for use in patients who meet the criteria specified in the proposed indication, Dr. Yang voted yes; Dr. Ku voted yes; Dr. Kang voted yes; Dr. Richardson voted yes; Dr. Becker voted yes; Dr. Byrne voted yes; Dr. Evans voted yes; Dr. Brem voted yes.

Question 3, do the benefits of the Pipeline Embolization Device for use in patients who meet the criteria specified in the proposed indication outweigh the risk of the Pipeline Embolization Device for use in patients who meet the criteria specified in the proposed indication, Dr. Yang voted yes; Dr. Ku voted yes; Dr. Kang voted yes; Dr. Richardson voted yes; Dr. Becker voted yes; Dr. Byrne voted yes; Dr. Evans voted yes; Dr. Brem voted yes.

On Question 1, the Panel voted 12 to 0 that the data shows that there is reasonable assurance that the Pipeline Embolization Device is safe for use in patients who meet the criteria specified in the proposed indication -- I'm sorry 9 to 0 -- 8 to 0 -- I'm sorry.

(Laughter.)

Okay. I will repeat that. On Question 1, the Panel voted 8 to 0 that the data shows there is reasonable assurance that the Pipeline Embolization Device is safe for use in patients who meet the criteria specified in the proposed indication.

On Question 2, the Panel voted 8 to 0 that there is reasonable assurance that the Pipeline Embolization Device is effective for use in

patients who meet the criteria specified in the proposed indication.

On Question 3, the Panel voted 8 to 0 that the benefits of the Pipeline Embolization Device for use in the pre-specified patient population do outweigh the risks of the PED for use in patients who meet the criteria specified in the proposed indication.

The three voting questions are now complete. We now need to collect the devices. Please pass the devices to the ends of the table for collection.

Thank you.

DR. HURST: I will now ask the Panel members to discuss their votes. If you answered no to any question, please state whether changes in labeling restrictions on use or other controls would alter your vote.

And I'd like to start with Dr. Byrne, please.

DR. BYRNE: It seemed clear to me that the device met the standard of reasonable assurance of safety and efficacy, and that was clear.

DR. HURST: Thank you.

Dr. Ku?

DR. KU: I'd like to congratulate both the FDA as well as the Sponsor for the way that they developed their protocol and the way that it was structured. The questions that they evaluated seemed to answer all the appropriate concerns.

DR. HURST: Dr. Yang?

DR. YANG: I felt that the data certainly supported the safety and efficacy. When asked to consider the risk/benefit ratio, given the condition and the lack of other current options, I felt that the risk/benefit ratio was quite reasonable.

DR. HURST: Thank you.

Dr. Brem?

DR. BREM: I concur that both the FDA, the company, and the family members who came were all to be commended on their professionalism and making it clear the benefit.

DR. HURST: Dr. Evans?

DR. EVANS: Is that punishment from yesterday?

(Laughter.)

DR. EVANS: After careful evaluation of all of the data, I decided I really like the color blue.

(Laughter.)

DR. EVANS: Let me first thank all the folks at Chestnut Medical Technologies and the FDA for their efforts. I realize that a lot goes into this evaluation, and I appreciate those efforts. At most of these meetings, I have to provide a detailed biostatistics lecture on why the data are not as strong as it's being purported to be. And I didn't have to do that today.

I think had some minor issues with the way some individual patient data was handled in the analysis, but it turns out that even under

alternative analyses, that, you know, those patients were so few and the data were so strong that it didn't affect the qualitative outcome of the interpretation. And so I think in this case the data spoke for itself. The data were strong.

DR. HURST: Thanks, Dr. Evans.

Dr. Kang?

DR. KU: The data presented were comprehensive and were interpreted conservatively, and in this setting, they met the criteria set out by the FDA.

DR. HURST: Dr. Becker?

DR. BECKER: The benefits are certainly clear, and the device is safe, so I don't think there's any questions.

DR. HURST: Dr. Richardson?

DR. RICHARDSON: I would like to commend the company and the FDA. This was an excellent presentation, very clear, very concise, and we have a very useful device on the market now. Thank you.

DR. HURST: Thank you, Dr. Richardson. I'd also like to commend the Sponsor, the FDA, and the patients who gave their time to appear here today, and obviously, a very good overall result. Thank you very much.

And I'd also like to ask Dr. Eydelman if she wishes to say anything additional.

DR. EYDELMAN: I also wanted to join you to thank everybody who came to the Open Public Hearing. We really appreciate your time, your efforts to come and tell us your respective stories.

Thank you, Panel, for making the time to come and share your thoughts, and your thoughtful deliberations were greatly appreciated. And thanks to my team for a terrific job once again. Thank you.

DR. HURST: The March 18th, 2011 meeting of the Neurological Devices Panel is now adjourned.

(Whereupon, at 2:40 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

NEUROLOGICAL DEVICES PANEL

March 18, 2011

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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CATHY BELKA

Official Reporter